

## THE BIOLOGY OF MENTAL DEFECT

# The Biology of MENTAL DEFECT

BY

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WITH A PREFACE BY

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## PREFACE

*Mental Defect*, a forerunner of this book, appeared in 1933. The first edition of the *Biology of Mental Defect* was published in 1949 and revised in 1953. A third edition is now needed. It is needed because of our greater knowledge. This knowledge is largely of details. In 1933 Professor Penrose described the then prevalent view that all mental defect was either due to injury or infectious disease, or to the "neuropathic diathesis", which is somehow transmitted from parent to child. He took the view, which he further developed in his report to the Medical Research Council in 1938, that inborn mental defect was due to a very great variety of causes. This is now universally accepted. Its acceptance has led to a curious result. Different workers have specialized in the study of different conditions, for example phenylketonuria, which requires biochemical techniques, and Down's syndrome (mongolism) which requires cytological techniques. Perhaps fewer all-round biologists are working on mental defect in general than were doing so thirty years ago. This is one reason why this book has no serious competitor.

The most sensational discovery about mental defect since the last edition is that not only mongolism, but several other conditions combining mental defect and physical abnormality, are due to cytological aberrations, the commonest being an extra chromosome. All told, they only account for a small fraction of mental defect, but they lead to a conclusion of great importance. A mongoloid is not an imbecile or idiot because he or she possesses abnormal genes in the cell nuclei, like an *epiloiac* or an *amaurotic idiot*, but because he or she has too many of certain normal genes. Penrose believes that many unclassified defectives are defective because, though cytologically normal, they have too many genes of a kind which are

found in most normal people, and are, on the whole, desirable in the heterozygous condition

We can just begin to see how the frequency of mental defect may be lowered. In the first place persons with certain dominant abnormalities should not have children. This is not to say that they should be compulsorily sterilized. However this would probably stop the birth of less than one per cent of defectives. Secondly the marriage of cousins should be discouraged. So should that of a relative of the father, of a defective believed to be homozygous for a gene increasing the liability of defect, with a relative of the mother. However within a century or less it may be possible to detect heterozygotes for most such recessive genes and discourage their intermarriage. When all the measures of which we can think at present have been taken we shall not probably have reduced the frequency of mental defect by more than about a quarter. We do not yet know how to prevent harmful mutations of genes or harmful rearrangements of chromosomes. On the contrary the governments of the most powerful states are increasing the frequency of such mutations by nuclear explosions, and sometimes by contamination of air and water from atomic power stations.

This does not mean that the problem of prevention is insoluble. The contrary is true. It is only thirty years ago that Folling, Penrose, Sjogren and a few others began not merely to identify single genes which are responsible for mental defect but to estimate their frequency in human populations, while Penrose and I first estimated human mutation rates. The complete or almost complete prevention of mental defect may require as much human effort as the achievement of mechanical flight, or the production of a nuclear explosion. And we do not know what sort of effort is needed. For example one of the important clues to the cause of mongolism came from Blakeslee's work on a plant, *Datura stramonium*. This ignorance makes it clear that any codification of our present knowledge is of value to all mankind. I could wish that this book were larger, but the bibliography is of very great value.

However a purely intellectual approach is not enough. Darwin was a great biological thinker and observer largely because he loved animals and plants, as is clear from his biography. In Sir Thomas More's Utopia (or rather Robinson's

translation of it from Latin to English) we read of the Utopians

"They have singular delite and pleasure io foles. And as it is a greate reproche to do annye of them hurte or iojury, so they prohibite not to take pleasure of foolyshnes."

In Utopia no one who did not love fools and treat them well was allowed the privilege of keeping one in his house. Professor Penrose genuinely loves fools. When I presented him with certain calculations he accepted them with every mark of interest and pleasure. Soon afterwards I saw him examining the drawings of a defective, and expressing the same emotions. He was right. It is perhaps more remarkable that a boy who can hardly speak should be capable of excellent drawing than that one professor should be capable of helping another to analyse his data. I suspect that in Utopia the normal people found the mentally defective amusing and played practical jokes on them. This seems to me a far more human attitude than imprisoning them, as is the practice in "advanced" states today. Penrose is perhaps Utopian in other respects than in his attitude to fools. That is to say it may take four centuries before his attitude is even as generally adopted as is that of Sir Thomas More on hunting in India or England at present.

I have only one warning to readers of the book. Penrose has the habit of presenting views, which he does not share, with scrupulous fairness. It is thus often necessary to read his book with care in order to discover what he thinks himself. In my opinion this is worth doing.

J. B. S. Haldane

## PREFACE TO THE 1948 EDITION

I AM greatly honoured by Professor Penrose's request that I should write a preface to his book. Human abnormality, whether of a desirable or undesirable type, tends to generate violent emotions which are unfavourable to clear thought. As much nonsense has probably been written about genius as about idiocy, and as many men and women have perhaps been killed because they were too good or too intelligent as because they were too bad or too stupid.

The demonstration that some cases of mental abnormality were largely genetically determined led to exaggerated hopes of eugenical improvement. The demonstration that others could be improved by hormones, psychotherapy, or special teaching methods led to equally exaggerated hopes of another kind. Both schools of thought underestimated the immense complexity of the problem. This was first concretely shown in Penrose's now classical report (Colchester Survey) to the Medical Research Council in 1938, in which he demonstrated that mental defect could be due to a vast variety of different causes. There is nothing surprising in this. Everyone knows that visual defect is due to many causes, and that some kinds can be improved by spectacles, others by surgery, while yet others are at present incurable, though the incurable fraction is slowly decreasing. The brain is a vastly more complex organ than the eye, and can go wrong in many more ways.

A casual reader might well be discouraged by the final chapter of the book. We cannot do so much about mental defect as had been hoped in the recent past. Nor could we do as much about flying four hundred years ago as Leonardo da Vinci had hoped. But there is no reason to suppose that one problem is any more insoluble than the other. The solution of the problem of flight

required the accumulation of a vast amount of data on very diverse topics during four centuries

We do not know what data will be required. But among them is certainly a knowledge of a great deal of normal human genetics. It must be emphasized that it is entirely normal to be the carrier of a recessive gene for some grave physical, chemical, or mental abnormality. Even where this is not so, the range of human variation is such that I believe very few normal married couples, if they could have a hundred children, would not have at least one seriously defective in one way or another.

At present we can neither stop such children from being born nor, save in a few cases, cure their abnormality. This is because we do not know how to do so. Even if we did, we might prefer to spend the necessary effort on the construction of greyhound tracks, jet propelled bombers, or nylon hosiery. But no amount of good will, or of bad will (for some programmes have been motivated by a hatred of abnormality similar to that which led to the burning of choreics for witchcraft), would greatly reduce the number of such children born at present, nor make them normal, though many of them could be socialized to some extent.

We do not know what kind of knowledge we need. It is entirely possible, for example, that a suitable hormonal treatment of elderly mothers could halve the frequency of mongolism, or that a common gene exists so closely linked with that for Huntington's chorea that a simple test would often enable us to state which children of a choreic carried the gene responsible for the condition and which could safely marry. Neither of these possibilities is very likely at present, but neither can be dismissed. They would equally be a part of eugenics.

Apart from its practical aspect I believe that the study of mental defect is of considerable philosophical importance. The question of why people are different or what determines their individuality is of the greatest interest, and to my mind is one of the questions which shows up the weakness of idealistic philosophies. It can be answered in a few cases. And the answers may be very surprising. "John Smith is a complete fool because he cannot oxidize phenylalanine" discloses a relation between mind and matter as surprising as transubstantiation, and a good deal better established. On the ethical side it raises



the problem of human rights in a rather sharp form. Has a hopeless idiot the right to life and care, though he or she is not a rational being nor likely to become one? If so, has a chimpanzee with considerably greater intelligence similar rights; and if not, why not? If not, where are we to draw the line? Hitler gave one answer; Penrose gives a very different one.

I hope therefore that this book will not only be read by physicians, but by social workers and even by one or two of the Members of Parliament and Peers who have to frame the law as to mental defect and criticize its present administration. I think that it may claim to be as much a contribution to general culture as a book on primitive human societies or on other forms of incomplete human achievement.

I do not agree with every statement in the book. I do not suppose that Professor Penrose will do so ten years hence, for our knowledge of the subject is growing very rapidly. However, he has weighed the arguments in each case very carefully, and I know of no one better qualified to form a considered judgement.

I hope therefore that his book will not merely be used as a text-book by specialists, but will be recognized as a contribution both to thought and to humanism.

J. B. S. Haldane

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## FOREWORD

Advances in medicine and in genetics have shown no signs of slackening since the 1953 revision of this book. Indeed, during the last few years, fresh discoveries have shattered many treasured concepts and opened entirely new vistas for research into the prevention and treatment of mental subnormality. A new edition is therefore indicated. As before, the first six chapters give a general account of the subject and the rest are concerned with special conditions. A great deal of the book has been entirely re-written with the invaluable assistance of Dr J. M. Berg who was, in particular, largely responsible for the preparation of Chapter X and of Miss Helen Lang-Brown in an editorial capacity. Professor Haldane has not only made numerous helpful suggestions but has also written a new preface.

Thanks are specially due to Mr S. Jayakar for his careful reading of the proofs, to Mr A. J. Lee for line drawings, to Dr J. R. Ellis for Plate VIII, to Miss Ruth Marshall for providing details for Appendix 10, to Dr G. G. Millman for Plate Va and to the British Medical Association for permission to reproduce Plate Vb.

August 1962

L. S. P.

## FOREWORD TO THE 1948 EDITION

IN my book on *Mental Defect*, published in 1933, an attempt was made to present the subject as one which provided great opportunities for scientific research. Methods suitable for application in this field were described and the social, medical and genetical aspects were distinguished. During the last fifteen years important discoveries have been made in medical genetics, many of which relate to mental defect and new information has been brought to light concerning the social significance of low intellectual capacity. Consequently a need has arisen for reorientation of teaching so that the problems of mental deficiency can be properly related to the rest of sociology and medicine.

The present book discusses mental deficiency from the point of view of human biology. The relevant subject matter is so varied and extensive that it would be presumptuous for any single writer to try to deal with every aspect in detail. Indeed, to do so adequately would be equivalent to writing large sections of text books on psychology, medicine, sociology and human genetics. To limit the task here medical and psychopathological conditions encountered in mental deficiency practice are discussed chiefly within the framework of genetics. Full clinical descriptions of important pathological types of defect are given but some of the rarer peculiarities are only mentioned briefly. Since my approach to mental defect here is primarily biological, the practical administrative aspect of the subject is only sketched. Enough of the historical and legal background is explained, I hope, to enable the student properly to appreciate the vicissitudes of the concept of mental deficiency.

Since the compilation of a complete bibliography was not practicable I have adopted the principle of providing references,

most of which fall under one of two headings. Works of historical or basic interest are cited and also some which are typical of recent researches. The reader's indulgence is requested if references to my own work are too frequently encountered. Many examples for demonstration purposes are taken from the Colchester Survey, carried out between 1931 and 1937 under the auspices of the Medical Research Council and the Darwin Trust, because these data were easily available to me. I wish to take this opportunity of thanking all those who have assisted in the task of preparing the manuscript of this book for the press, and, in particular, Miss Helen Lang-Brown. Some of the photographs were kindly supplied by Mr. H. Goodfellow and others by Dr. E. D. Taylar. I am much indebted to Professor J. B. S. Haldane and to Dr. E. O. Lewis for their helpful suggestions

L.S P.

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## CHAPTER I

### HISTORICAL BACKGROUND

*Introduction—Early History—Extension of the Concept of Defect—Mental Measurements—Comparative Nomenclature—Mental Defect as Social Incompetence—Defect and Instability—Recent Legislation—The Biological Viewpoint*

#### INTRODUCTION

MEN and women are not all alike in physical stature. Most of them vary within the limits which define a group popularly described as normal or average. A few are noticeably tall or noticeably short. In extreme instances divergence from the normal is so great that the man or woman qualifies to be called a giant or a dwarf. The same is true of intellectual stature. The bulk of the population is said to have normal intelligence but, undoubtedly, as with stature, a great deal of variation exists. Outstandingly clever people and very dull people are to be found in the normal population. There are also giants and dwarfs of intellect. The one extreme has been exemplified by men of genius like Newton, Mozart and Darwin. The other extreme is represented by idiots who, in the most profound cases, can scarcely be credited with any mental processes at all.

Variation between individuals who are members of the same animal species is a biological rule to which the human race shows no exception. Degrees of mental capacity are more noticeable and probably have a wider range in man than in animals. Domestic animals, such as dogs, vary in mental ability, but the differences are difficult to measure. In man, unfortunately, very low degrees of intelligence are much more frequently encountered than the very high degrees at the other end of the scale, according to our ordinary, rather arbitrary, units of measurement. A great proportion of intellectual dwarfs do not survive childhood, indeed, many of them do not even survive earliest infancy. In spite of this, the actual numbers

remain very large and this group may be at least as significant biologically as the group formed by the intellectually brilliant

### EARLY HISTORY

A study of the history and growth of knowledge is helpful in acquiring a balanced outlook on the problem of intellectual defect. A useful source of historical information is the text-book by Barr (1904). In early times it seems probable that only the grossest examples of mental defect were considered remarkable. Even at the present day we find that, in any community where relatively little attention is paid to mental health, only the severest cases, idiots and imbeciles, are recognized. It is natural that provision for the care of these should be the first step when hospital accommodation is very limited.

The term "idiot", which signifies only the most extreme cases of mental defect, formerly applied to the whole class of defectives. It is derived from a Greek word for a person who did not take part in public life. The same root is found in "idiom" and "idiosyncrasy". Originally the term applied also to untrained, ignorant or lay people, and it was used in this sense as late as the seventeenth century. "Imbecile", derived from the Latin *bacillus*, a stick, has always implied weakness, originally in a predominantly physical sense.

The early history of the subject is obscured by lack of discrimination between congenital physical deformity, such as produces cripples or dwarfs, and mental incapacity. Moreover, epileptics, psychotics and deaf mutes have been frequently confused with the intellectually defective. The fact that a variety of conditions can coexist in the same individual often makes clinical analysis difficult even at the present time.

The ancients appear usually to have regarded idiots with aversion. In Sparta, under the laws of Lycurgus, the mentally defective probably shared the fate of other weakly infants, who were allowed to perish from exposure or were thrown into the river Eurotas. Among primitive peoples of the present day similar practices have sometimes been reported. The modern equivalent, politely called *euthanasia*, was carried out under the Nazi regime in Germany. There were ancient Roman laws which provided for the killing of malformed or weakly children, though defectives were tolerated in Rome if they had value

for amusement or diversion. In mediaeval times superstitions connected with witchcraft often determined harsh treatment for defectives. Some imbeciles were believed to be changelings without human souls. The rise of Protestantism did not at first improve their position. Apparently Luther (1576) subscribed to the contemporary belief that the Devil was the father of idiots. It is recorded that on one occasion he recommended that a 12-year-old defective girl be drowned. His associates, however, appear not to have shared his opinions on this point.

While some interpreted the mutterings of idiots as conversation with the Devil, others believed them to be evidence of divine inspiration. In many communities defectives were regarded as especially innocent and holy. This attitude seems to have been more characteristic of Eastern than of Western cultures in early times. Both Confucius and Zoroaster in their writings instructed their followers to care for the weak-minded, to clothe them and to treat them kindly. The advent of Christian humanitarianism tended to raise the status of defectives in Europe. Under the rule of Constantine, the Bishop of Myra (the original Santa Claus) is said to have advocated protection of idiots. They may have often been given homes in monasteries. It is interesting to note that, during excavations on the site of a ninth century monastery at Breedon in Nottinghamshire, Brothwell (1960) found a skull probably identifiable as that of a mongolian type of imbecile. The term *cretin*, which is still used in France to cover many kinds of idiocy, is merely a corruption of *chretien*, meaning Christian. The expression *les enfants du bon Dieu*, commonly applied to defectives, represented the same point of view. In England the early approach to the subject was more objective and, in the reigns of Edward I and Edward II, legislation was enacted to provide for the elementary management of an idiot or "born fool" (*fatuus naturalis*) and of his estate. A defective, moreover, was at that time distinguished from an insane person, whose mental capacity could fluctuate (*non compos mentis sicut quidem sunt per lucida intervalla*).

The medical and scientific study of defect began with the acceptance of defectives as belonging to the rest of humanity. Idiots are, in fact, members of the human race and, to a large extent, inevitable variants of the human species. Hippocrates described anencephaly and some other kinds of cranial de-

formity associated with severe defect. The inability of medicine throughout the ages to supply any plausible explanation for inborn defects or to suggest any remedy, however, left the door open to superstitious speculation for many centuries. Philosophers and psychologists had little more than platitudes to offer. "The Defect in *Naturals*", wrote Locke (1689), "seems to proceed from Want of Quickness, Activity, and Motion in the intellectual faculties, whereby they are deprived of Reason." However, Locke did distinguish between defect and insanity. "In short, herein seems to lie the Difference between Idiots and Madmen, that Madmen put wrong *Ideas* together, and so make wrong Propositions, but argue and reason right from them, but Idiots make very few or no Propositions, and reason scarce at all." Early clinicians were less precise. "Ideotism", defined by Pinel (1806) as "total or partial obliteration of the intellectual powers and affections", was applied to cretins and other defectives and also to insane catatonic or stuporose patients.

Soon after the French Revolution, Itard's (1798) treatise on the wild boy of Aveyron initiated the practical scientific study of the psychology of defect. An unsuccessful attempt was made to educate a youth who had been found wandering in the forest. *Juvenis Aveyronensis* was the appellation supplied by the local professor of natural history, to conform with descriptions advocated by Linne, such as *juvenis lupinus Hessiensis*, 1544 (a young man found in Hesse among wolves) or *juvenis ovinus Hibernus* (a young man found among wild sheep in Ireland). Using methods established by Periere for training deaf-mutes, Itard was unable to educate his savage. However, he gave the first clear account of the psychology of a mentally defective person. The effect was to stimulate others to study the problem of educating the weak-minded, to find the potentialities of these unfortunates so that the best use could be made of their meagre mental resources. Séguin, a pupil of Itard, founded, in 1837, a school for idiots in Paris. He was able to satisfy Pinel and Esquirol that it was worth while to pay more attention to defectives than had hitherto been thought necessary, and he was invited to apply his principles of training at the Bicêtre hospital. Thus, in keeping with the reforms which had been introduced into treatment of the insane by humanitarian psychiatrists, the status of the mentally defective was also raised. Esquirol re-



ferred to Seguin's mission as the removal of the mark of the beast from the forehead of the idiot

Soon afterwards the need for providing special institutions for those persons who were obviously idiots was recognized in England. The training and care of these individuals was considered an eminently suitable object for charity. The philanthropist Andrew Reed expressed, in 1840, the hope that he might be allowed to do something for fellow creatures who were separate and alone but with "the Divine image stamped upon all". Largely owing to his efforts, the first asylum for idiots in England was founded at Park House, Highgate. It was a charitable institution under the patronage of Queen Victoria and the Prince Consort. "The principle which rules", said Reed, "is charity—Divine Charity". The success of the institution was so great that expansion was soon found necessary, and in 1849 Essex Hall, Colchester, was started as an annex for nearly a hundred patients with a view to teaching them simple mechanical employments. The remaining patients at Park House were all transferred to a newly built "model asylum" at Earlswood, Surrey, in 1855.

At about the same time Guggenbuhl, whose sympathies had been specially aroused by the needs of the cretins and other dwarfs, common then in Switzerland, founded a training school for all types of idiots near the summit of a mountain close to Interlaken. It was thought that the pure atmosphere and the glorious panorama of nature's wonders at this site would help to awaken the dormant minds of the patients. As it turned out, Guggenbuhl had promised too much. Ultimately his institution had to be closed and he himself was officially condemned as a charlatan. In spite of this, the impact of his philanthropic and experimental enthusiasm was felt in many countries. A more sober influence was that of Saegert in Berlin, who had formerly trained only deaf-mutes. He transferred his attention to the education of idiots and, in 1846, his monograph on the cure of imbecility by intellectual means was published. In Saxony the persuasive powers of Ettmüller in 1844 led to the foundation of the first German state institution for the training of idiots, somewhat characteristically, attendance was made compulsory by law. Nevertheless, nearly all the institutions which sprang into being in Europe during this period were private organiza-

tions. They were usually charitable foundations, like the Alsterdorfer home near Hamburg, started by a minister of religion, Sengelmann, and administered by an unsalaried director.

In the United States a Commission was appointed in Massachusetts to enquire into the condition of idiots, under the chairmanship of Dr Samuel G. Howe, famous for his education of the blind deaf mute Laura Bridgman. A similar commission was appointed in New York, with the result that, shortly afterwards, in both states, schools were opened in 1848. The teaching of defectives was modelled upon the European methods and Seguin was invited to assist in its development. In Pennsylvania, soon afterwards, the Elwyn Training School was opened, and, again, the directors received advice from Seguin, thus ensuring that the traditions of the earliest pioneers were maintained. In Ontario, Canada, an institution with similar objectives was started at Orillia in 1859.

Judging from the early reports of cases and the descriptions of training plans, most of the educational work was carried out on subjects who now would be considered to be severely subnormal and to fall into the categories of idiots and imbeciles. That is to say, they were mostly ineducable in the ordinary scholastic sense, though many were able to be taught to converse, to be clean in habits and to enjoy simple games and occupations.

#### EXTENSION OF THE CONCEPT OF DEFECT

During the latter half of the nineteenth century the scope of training programmes was gradually extended to include the large number of cases of mental subnormality whose capacities lay between the level of the imbecile and the normal range. The first investigator accurately to distinguish this group from the more severely handicapped appears to have been Duncan (1860), who wrote as follows in a report to their benefactors:

"For all practical purposes the objects of your Charity may be divided into three classes—simpletons, imbeciles and idiots. The first are those feeble minded who have not been able to receive instruction in the ordinary manner, who do not possess experience in life peculiar to those of their age in their social position and who are said to be 'dolt', 'stupid', and 'fool', by the uncharitable. They have nearly all the faculties to a

certain degree, but indicate their alliance to the true idiot by their physiological deficiencies and general inertia of mind. They are to be distinguished from the backward and ill taught and unfortunately cannot always be said to be quite sane."

Simpletons were all educable to some extent and their inclusion widened the scope of the treatment of mental deficiency. The question of providing education for defectives began to merge into the ordinary scholastic problem of how to give the best training to backward children. The new problem was of quite a different nature from that encountered in institutions where the children cared for could not be expected to take part in normal community activities. However, a great many simpletons, when trained, should be able to carry on as ordinary citizens. To achieve this end, special day schools for the education of simpletons were founded in many countries. In England, the Idiots Act of 1886, which provided for the care of idiots and imbeciles, was followed by the establishment of special schools by law in 1896. Mentally defective children between the ages of 7 and 16 were further provided for under the Elementary Education Act of 1899. In Italy, where provision for idiots had been tardy, day schools for training defectives, on principles advocated by the enthusiastic pupils of Montessori, were set up in several urban centres about the year 1899.

A British Royal Commission was appointed in 1904 "to consider the existing methods of dealing with imbeciles, feeble-minded or defective persons not certified under the Lunacy Laws". After four years the Commission (1908) reported that there existed in the community large numbers of these mentally defective persons whose training was neglected and over whom insufficient control was exercised. Many were committed to prisons for repeated offences; many who did not require treatment were to be found crowding the lunatic asylums; and also many were at large, both adults and children, who, in one way or another, were incapable of self control and therefore exposed to constant moral danger. The Commission recommended the creation of a system whereby these mentally defective persons could at an early age be brought into touch with some friendly authority, trained as far as need be, supervised during their lives in cooperation with their relatives, or detained and in some measure treated as wards of the State.

The Mental Deficiency Act, passed in 1913, and amended in 1927, embodied the main recommendations of the Commission. Definitions were laid down for administrative purposes, although they were of little biological significance. For general purposes, "mental defectiveness" was defined as "a condition of arrested or incomplete development existing before the age of eighteen years, whether arising from inherent causes or induced by injury". Four subdivisions were specified, idiots, imbeciles, feeble-minded persons and moral defectives. In practice, the category of moral defect was rarely used and the differentiation of the other three types was more often made on grounds of intellectual level than upon agreement with the legal description. In the case of the feeble-minded, however, what the interpretation of the Acts usually insisted upon was that no adult could be certified in this class unless the need for care, supervision and control was combined with insufficient protection for themselves or for others. Defectives of any age who were found neglected, abandoned or otherwise in need of help, as well as those found guilty of criminal offences, were dealt with by the Local Mental Deficiency Authority.

Less elaborate legal definitions are found to be efficient in the United States and Canada. The Mental Hospitals Act of Ontario (1937) defines "mental defective" and "mentally defective person" as "a person in whom there is a condition of arrested or incomplete development of mind, whether arising from inherent disease or injury, and who requires care, supervision and control for his own protection or for the protection of others".

In England and Wales, the Education Act, 1921, defined mentally defective children as those incapable of receiving proper benefit from instruction in the ordinary schools by reason of a defect of mind.

The Education Act, 1944, and the subsequent regulations issued by the Ministry of Education, placed responsibilities on Local Education Authorities for the provision of suitable education for children suffering from disability of mind or body. The Local Education Authority now has the duty of ascertaining all children, over the age of 2 years, who require special educational treatment. The Ministry defined as *educationally subnormal* any pupil who, by reason of limited ability or other

conditions resulting in educational retardation, requires some specialized form of education wholly or partly in substitution for that normally given. This category includes not only children who were, in the past, *certifiable* under the Education Act, 1921, but also dull children who are retarded in their school work by reason of "limited ability", and those who are backward in the basic subjects because of "other conditions". The term mental defect was no longer applicable to a child considered educable within the education system. However, children formerly *certifiable* would now be *ascertained* as educationally subnormal, and placed in Special schools or classes, with compulsory attendance up to 16 years of age. Children so ascertained would usually come within the 50 to 70 I.Q. range. Tests which measure scholastic ability are essential to diagnosis. In practice, nevertheless, a child's behaviour pattern tends to influence the assessment.

#### MENTAL MEASUREMENTS

It was not until after the invention of standardized intelligence tests that the true nature and extent of the problem of training the simpletons became apparent. Galton (1869) was among the first to suggest distributing intelligence, like other human characters, on a linear metrical scale ranging from idiocy to genius. He did not distinguish between potential capacity and actual academic or social success and he considered reputation to be an accurate measure of ability. One method is demonstrated in the following example, where he (Galton 1889) distributed 1,000 medical students in five classes according to academic records supplied to him. He rated 28 men distinguished, 80 considerable, 616 moderate, 151 with very limited success and 125 as failures. He made these comments: ". . . of the successful men, within fifteen years of taking their degrees, stood three Professors of Anatomy, . . . towards the bottom of the failures lay two men who committed suicide under circumstances of great disgrace, and the lowest of all . . . was hanged."

Intelligence, as measured by Binet and Simon (1907) and by the more recent revisers of this test, was by intention closely related to scholastic success. The test provided a rapid method of ascertaining how many children in the population would need special education. It was primarily designed as an aid to

teachers in the allocation of pupils to their correct grades or classes in schools. It was therefore scored in years and months of mental age. By comparing the mental age with the chronological age, it could be seen at once whether a child was advanced or retarded. Since success later on in life is closely related to educational aptitude, children who would be likely ultimately to be economic or social failures in a competitive society could be identified at an early age. It soon became apparent that the number involved in this class was very large. In the United States, where psychologists and sociologists expended great energy on the problem, the group of mentally subnormal people grew to prodigious proportions. Eventually the name "moron" was coined by Goddard to denote roughly the class described as simpletons by Duncan and subsequently called feeble minded in England because the term "simpleton" was thought to be derogatory.

#### COMPARATIVE NOMENCLATURE

It is convenient here to digress from the presentation of historical facts and to draw attention to the nomenclatures which have developed in different countries to describe the grades of defect. Confusion is apt to arise with the terms "high grade" and 'low grade', which are widely used to connote relatively mild and severe cases respectively i.e. a high grade case is a mild one. Sometimes these terms are used to qualify cases within larger groups. For example, high, medium and low grade imbeciles are occasionally differentiated for descriptive convenience. An important point to note is that, in the United States, the term 'feeble minded' has been applied to the whole class of defectives whereas, in England, its use is restricted to the relatively high grade patients. Scandinavian and German usage has favoured the expression "*oligophrenia*" to describe all types of mental defect. Several authorities in England and America also have recommended the general adoption of this cumbersome word. Other terms that have been used to mean the same thing are "amentia", "anergasia", 'psychasthenia' and "phrenasthenia".

For purposes of euphony the term "mental subnormality" has lately been introduced to cover all grades of defect in England. The severely mentally defective are now called

severely subnormal. The mild or high grade mentally defective are officially called "subnormal". This term causes confusion because it also applies to all grades. In America the general designation "mental retardation" is preferred. According to the recommendations of the American Association on Mental Deficiency, there should be five levels of measured intelligence and the lowest, formerly called idiocy, could now be called profound subnormality. Imbecility would be divided into two classes, moderate retardation and severe retardation. Mild subnormality could be substituted for the unsatisfactory term "moron" and there would be a borderline group which implied proximity to the normal range.

The roughly equivalent designations used in different countries are shown in Table I, together with the approximately corresponding Binet intelligence test levels. Since children of different ages have to be compared, the Binet test score is usually expressed in the form of the intelligence quotient, or I.Q., an index which is almost independent of age between about 5 and 13 years. The intelligence quotient is defined as the measured mental age expressed as a percentage of the chronological age at the time of testing. For adults the intelligence quotient is not a valid concept. A fictitious base of about 14½ years of chronological age has to be used when the I.Q. of an adult is estimated. Some authorities prefer a base of 16 years and others use 14 years. Binet test scores for adults are therefore best expressed only as mental ages.

There are special difficulties which arise in describing people who are thought to be almost, but not quite, defective. Such terms as "mentally subnormal but not defective", "borderline" (*grenzformen*), or "mentally dull", "scholastically retarded" and "poorly gifted" (*schwach begabt*) have been frequently employed, but their connotations are rather indefinite. In the early days, when only the idiots and other clearly abnormal cases were recognized, these distinctions between the different classes of higher grades did not come into consideration. There is fair agreement that the upper limit of idiocy should be set at a mental age of 3 years, or an I.Q. of about 20. The distinction between the imbecile and the feeble-minded, or moron, is less certain. The I.Q. of 45 is often used in England, whereas that of 55 has been suggested in America. Much depends upon the actual tests

TABLE I

TRADITIONAL NOMENCLATURE FOR THE MENTALLY SUBNORMAL

Degree of Defect	British	American	French	Approximate Binet Intelligence Level	
				I Q (children)	Mental Age in years (adults)
Mild (high grade)	Feeble minded	Moron	Debile	50-69	7-10
Severe (medium or low grade)	Imbecile	Imbecile	Imbécile	20-49	3-6
Severe (low grade)	Idiot	Idiot	Idiot	0-19	0-2
All Grades*	Mentally defective mentally handicapped mentally subnormal	Feeble minded mentally retarded	Arrière oligophrénie	0-70	0-10

\* The terms Schwachsinn, Geistesschwache and Oligophrenie are used in Germany

used for measuring intelligence. The absolute upper limit of deficiency is commonly set at about the I Q of 70, but this criterion is subject to wide variations of interpretation. Some German authorities do not recognize the distinction between imbeciles and feeble minded and place the upper limit of idiocy at a somewhat higher level than the mental age of 3. For instance, Weygandt (1936) considered that defectives should simply be divided into imbeciles and idiots according to whether or not they were capable of doing useful work (*geschäftsfähig*). The distinction between the borderline case and the normal, at an I Q of about 85, is never clearly defined because in this region the recognition of defect is based entirely upon the subject's social capabilities and these are not easily expressible in terms of mental age.

#### MENTAL DEFECT AS SOCIAL INCOMPETENCE

A new attitude became prevalent at the beginning of the twentieth century, engendered by the appreciation of the large



numbers that comprised the "moron" class. The defective was no longer an innocent sufferer deserving only pity. He was gradually becoming recognized as a menace. The growth of this idea has been well outlined by Davies (1930). "Morons", wrote Goddard (1914), "are often normal looking, with few or no obvious stigmata of degeneration, frequently able to talk fluently; their conversation, while marked by poverty of thought or even silliness, nevertheless commonly passes as the result of ignorance . . . yet they are the persons who make for us social problems." He stressed the close relationship of mental defect to pauperism, crime, intemperance and disease. The frequency of morons in the general population was estimated to be about 2 per cent but, among delinquents, paupers and those socially incompetent in other ways, the corresponding frequency was alleged to be 50 per cent. It thus became plain that mental defect was closely related to social incompetence. This realization led to a view of the subject which is generally accepted at the present time, namely, that whatever may be the individual's basic capacities, he is not considered to be mentally defective so long as he is socially acceptable. Legislation and practice have both supported this attitude.

An authoritative statement on this question was made in the British Report of the Joint Committee of the Board of Education and the Board of Control (Wood report) in 1929, where a mentally defective individual was defined as "one who by reason of incomplete mental development is incapable of independent social adaptation". The Committee who prepared the report made the concept of mental defect more comprehensive than previous authorities had done, and they drew attention to a group of families in the population, amounting to 10 per cent who were alleged to be socially incompetent. They considered that most defectives, especially the feeble-minded or morons, originated from this lowest social group. The group was stated to include, "as everyone who has extensive practical experience of social service would readily admit", a much larger proportion of mentally defective and insane persons, epileptics, paupers, criminals (especially recidivists), unemployables, habitual slum dwellers, prostitutes, inebriates and other social inefficients than the remaining 90 per cent.

In corroboration of this outlook, Lidbetter (1933) published

a large amount of data, which he collected in the course of social work, indicating that family groups of low economic status existed in the community. He showed that pauperism and poor mental and physical health were associated in many branches of these families and left the inference to be drawn that all these things were biologically inherited. Part of the association of these disabilities, however, seems to be due to the non biological social law of inheritance of wealth, this also implies conversely the inheritance of poverty in the same, non biological, sense. Poverty used to involve diminished opportunities both for scholastic education and social training and also inadequate medical care. This point was not overlooked by Isserlis (1923) who attributed the low intelligence which he found in children poorly fed and clothed at least in part to the unfavourable environment associated with low economic status. The idea that 10 per cent of the population is economically deficient, that is living in poverty, had its background in the social studies of Rowntree (1906) and of Bowley and Hogg (1925). The assumption that this part of the population formed a "social problem group", as understood by Blacker (1934) and others, in which hereditary mental defect was the characteristic feature, was not made by the earlier investigators. If mental defect is to be defined in terms of social incompetence, those relatively incapable of maintaining themselves economically in a competitive society are, by definition, mentally defective. The inference that the same people would be incompetent in a different environment or according to different standards is unjustified. The relativity of our judgments about mental capacity and their dependence upon social valuation has been again stressed by Lewis (1951).

According to current British practice, mental measurements and clinical examinations are only relevant in so far as they help to decide the probable social value of a patient. In America a similar view is also widely held and Fernald's ten points are sometimes used as a guide rather than any single measurement. Under Fernald's (1917) system the physician must ascertain the patient's standing with respect to (i) physical examination, (ii) family background, (iii) developmental history, (iv) school progress, (v) examination in school work, (vi) practical knowledge, (vii) social behaviour, (viii) industrial efficiency, (ix) moral

reactions, and (x) intelligence measured by psychological tests, before deciding whether he may rightly certify the subject as mentally defective. It is possible to devise measurements of social competence and Doll (1935) recommended the use of a rating scale which can be scored in terms of social age. If social competence is held to be the decisive criterion, it is logical to attempt its measurement though the task is beset with serious difficulties.

To the sociologist it may be an advantage to have a social criterion for defining a group, but to the biologist or psychiatrist such a definition is extremely unsatisfactory. Social criteria are not only changeable, they are relative, not absolute. Thus in a rural community scholastic defect is much less of a handicap than in a city. The requirements for success in industrial or commercial employment are very different from those on a farm, a quarry or a ranch. A good fisherman, herdsman or lumberman need not have many scholastic attainments, and if such workers were selected on account of scholastic successes, the results would probably be disastrous. A person whose abilities are entirely confined to clerical work is likely to be a failure in a community where manual work is the only means of livelihood. Not improbably, the gradually increasing importance of industry and commerce and of clerical and other technical occupations during the last hundred years has been a decisive factor in bringing the problems of educational subnormality and of feeble mindedness into the foreground. Idiocy and imbecility are defects sufficient to cause social failure in an agricultural community, but the scholastically incompetent person is especially likely to be a social problem in an urban community.

#### DEFECT AND INSTABILITY

There are other causes of social failure of quite a different nature. It is convenient though not absolutely free from logical error to distinguish between intellectual defect and emotional instability. Instability can be slight and accepted as within the normal range of behaviour. It can, however, be great enough to be classed as mental illness or derangement. The symptoms of mental illness include neurotic manifestations, hysteria, obsessions, psychopathic personality, depression, mania, paranoia,

schizophrenia, confusional states, organic dementia and epilepsy. Any of these conditions may occur as co existing phenomena in cases of mental defect. In some instances they may be part of the same disease process which has also caused the defect, and, when this is so, clinical differentiation of the co existing defect and instability may be impossible. Mental illness is undoubtedly a frequent cause of social failure. If it appears early in life, say before the age of 18 years, it is liable to be classed as intellectual defect from the administrative point of view. Indeed, selection of cases for institutional treatment is strongly biased by the tendency to remove from the community just those cases of defect in which symptoms of instability are also present. Thus the criterion of social failure—so simple and practical from the sociological and administrative points of view—leads to unreasonable complications when the matter is considered from the aspect of medical or biological science. The danger of confusion is not great if consideration is limited to idiots and imbeciles but, in the discussion of feeble mindedness or of the "moron", the great variety of standards on which social failure may be judged must constantly be kept in mind.

#### RECENT LEGISLATION

In 1954, a Royal Commission was appointed to enquire, "as regards England and Wales" into all aspects of the existing law and administrative machinery governing the certification, care and supervision of mentally ill and mentally defective persons. The Commission's deliberations were guided by the principle that treatment and care should be provided for mental patients with no more restriction of liberty or legal formality than is applied to patients who need treatment and care for physical diseases. Compulsory powers should be used only if it was necessary to override the patient's unwillingness, or that of his relatives, in the interests of the patient's own welfare or for the protection of others. In order to achieve these ends entirely new legislation was recommended in the Report presented in 1957.

A new Mental Health Act, based upon the suggestions of the Commission, was passed in 1959. The Lunacy and Mental Treatment Acts of 1890 to 1930 and the Mental Deficiency Acts, 1913 to 1938, were repealed. A detailed study of the 1959

Act and a summary of mental health legislation in England has been made by Edwards (1961). The main feature of the new Act is to allow much greater elasticity than formerly in dealing with patients. Fresh definitions of mental illness and mental defect were introduced which are purposely less specific than the earlier ones.

The term "mental disorder" has been introduced to cover every kind of disease and defect of the mind. The result is somewhat confusing for "disorder" suggests (and is used to designate) acute illness and insanity rather than intellectual defect. Two grades of mental subnormality are defined as types of disorder. One is "severe subnormality", a state of arrested or incomplete development of mind which includes subnormality of intelligence and is of such a nature or degree that the patient is incapable of leading an independent life. This definition approximately covers idiocy and imbecility. It is probably intended to include also that group of the feeble-minded with I.Q. below 60 (Lewis 1957). "Subnormality" by itself, means a state of arrested or incomplete development of mind (not amounting to severe subnormality) which includes subnormality of intelligence and is of a nature and degree which requires or is susceptible to medical treatment or other special care or training of the patient. This roughly covers the feeble-minded group though, presumably, idiots and imbeciles who responded well to treatment would also be included. The old category of moral deficiency is abolished and replaced by the concept of "psychopathic disorder", a persistent disorder or disability of mind, which results in abnormally aggressive or seriously irresponsible conduct on the part of the patient, and requires or is susceptible to medical treatment. This psychopathic designation is not dependent upon the intelligence level of the subject.

The new Act is bold and in some ways experimental. It can expedite treatment of both the mentally ill and the mentally defective and help towards the complete removal of stigma from these classes of patients. In particular, it crystallizes the modern attitude that, as far as possible, admission to hospitals for the mentally disordered or subnormal should be informal, avoiding the objectionable procedure of certification. Compulsory detention is made dependent on medical recommenda-

tion only and no longer requires a magistrate's order. Further, such detention is permissible in any hospital and not, as previously, restricted to specially designated hospitals.

The introduction of a new terminology, however, in which intellectual subnormality is classed as a disorder rather than a defect and in which there is a "severe" category but no corresponding "mild" category of subnormality, is untidy and illogical. Presumably one of the objects of these changes is to avoid rigid categorization of patients since this might tend to discourage attempts at treatment and rehabilitation in certain instances. Medical scientific classification, however, can be made more difficult when established terms have their meanings altered by law. In this book we will retain the use of the terms idiot and imbecile in their traditional senses and use "mild subnormality" instead of "subnormality not amounting to severe subnormality". We also do not refer to "intellectual subnormality" as a "disorder" of mind.

#### THE BIOLOGICAL VIEWPOINT

From what has been said it is now easy to see that a question such as "What is the cause of mental defect or subnormality—is it inherited and, if so, to what extent?" cannot be answered directly. The person who asks such a question exposes his ignorance by his underrating the complexity of the biological subject matter. In practice, mental defect is closely related to social incompetence. Hence, to obtain a proper understanding of mental defect, the conditions, which have led to social failure in people classified as subnormal or defective, must be analysed. The biological, psychological and medical significance of each factor must be examined separately. The aim in the present book has been to try to do this and at the same time to discuss the methods by which such analysis can be carried out. Since many of the conditions leading ultimately to social failure are found in the early life of the individual, sometimes before his birth, the study of genetics will play an important but by no means exclusive part in their description. Social scientists, whose preoccupation is with economics, law or political philosophy, are liable to forget that man is an animal and to neglect the biological problems which underlie the structure of human society. No apology is needed for making an attempt to redress

the balance by emphasizing the importance of human biology in the elucidation of the phenomena of mental defect. The usefulness of the biological attack on these problems was first demonstrated by the work of Punnett (1917) who applied the methods of population genetics (see Chapter V). He described how it was possible, on the basis of simple genetical assumptions, to predict future trends under the action of natural or artificial selection. His type of analysis can be extended to cover a large number of separate clinical conditions. This way of thinking enables us also to appreciate the significance, in the human race, of gene mutation and chromosomal aberration. Before beginning a detailed clinical and genetical survey, however, more must be said about the definition and extent of the field and about the social and psychological background of the modern concept of mental subnormality.

## CHAPTER II

### INCIDENCE, DEFINITION AND MEASUREMENT

*Crude Incidence—The British Royal Commission of 1904—The Survey of 1929—Comparison with other Surveys—Distribution of Intelligence Test Scores—Male and Female Distributions—Intelligence and its Measurement—Cultural Differences in Intelligence—Sense Deprivation—Physical Measurements—Head Size and Brain Weight—General Physique—Stigmata of Degeneration—Dermatoglyphs—Mental Defect and Socio Economic Status—Military Criterion of Defect*

#### CRUDE INCIDENCE

STATISTICS are available in many different countries showing the number of persons assigned to institutional care under the category of mental defect. Great discrepancies are noticeable when the returns of different countries are compared with one another, and they represent social rather than biological variations. In any locality the number of cases recognized is closely related to the provision of institutional beds. The extent of such provision, in its turn, depends upon the attitude of the civilization concerned towards defectives, the wealth of the citizens and their desire to use their means in this particular way. The number of beds provided never exceeds a small fraction of the number of persons who could reasonably be classified as defective, if so desired. Hence a statistical return of recognized cases must not be taken as a measure of the actual biological frequency of mental inferiority in a given population. The very reverse may be true, namely, that, unless the general level of intelligence is high, only a few of the most pronounced cases of defect are differentiated from the normal population.

A great deal depends upon the legal definition in force in the area concerned. Beyond this the manner of interpretation of laws is subject to local practical needs. In many countries no specific differentiation is made between defective and psychotic patients and, even where such distinction is made, as in Eng



land, many cases of defect drift into hospitals for the mentally ill. Furthermore, other types of institutions, such as homes for paupers, for the infirm or for the destitute, as well as prisons and reformatories, contain varying proportions of defective inmates; subnormal children also occupy beds in paediatric hospitals. Sometimes charitable or private institutions do not supply data for official statistics. Table II shows samples of figures, collected from the official reports referring to the year 1935 or, in some cases, a slightly earlier year (Penrose 1939c). The incidence of certified defectives varied from zero to over 1 per thousand. It ran parallel, though somewhat irregularly so, to the incidence of patients certified insane. In countries where relatively few beds, i.e. less than 2 per thousand of the population, were provided for every type of mentally abnormal person, little attention was paid to mental defect as a separate

TABLE II  
STATISTICS OF MENTAL HOSPITAL BEDS

Country	Approximate Population (in millions)	Inmates of Institutions for the Mentally Abnormal (about 1935)			
		Numbers (in thousands)		Incidence in Population (per thousand)	
		i	d	i/n	d/n
		Insane	Defective	Insane	Defective
England and Wales*	40.00	150.3	38.8	3.75	0.97
Scotland . . .	5.00	18.4	2.9	3.78	0.58
Denmark . . .	3.70	9.2	5.4	2.47	1.46
U.S.A. . . . .	127.50	409.6	80.4	3.21	0.63
Switzerland . .	4.15	13.4	2.1	3.21	0.51
Canada . . . .	11.00	30.6	7.7	2.80	0.70
Germany . . .	66.40	130.5	28.9	1.96	0.44
France . . . .	41.80	86.3	10.4	2.06	0.25
Norway . . . .	2.80	5.4	0.3	1.93	0.11
Italy . . . . .	42.20	75.1	8.3	1.77	0.20
Finland . . . .	3.67	6.0	0.0	1.62	0.01
Japan . . . . .	97.70	15.6	0.7	0.16	0.01

\* Corresponding figures given for Mental Hospital Beds in England and Wales for 1960 are, in thousands, 151.9 for mental illness (3.3 per thousand) and 59.8 for mental subnormality (1.3 per thousand). The incidence figure for mental illness has fallen and that for subnormality has increased (*A hospital plan for England and Wales*, London: H.M.S.O., 1962).

entity In such circumstances, there may be no separate hospitals for subnormals Even in countries which make considerable provision for defectives there remains the problem of how to deal with patients who are psychotic or epileptic and also defective These patients are often classified primarily as insane or epileptic, as this is considered the major factor of importance, and there are unavoidable ambiguities in the interpretation of such figures

The true incidence of mental subnormality in a general population can only be ascertained by a survey directed specifically to that end The actual numbers ascertained will depend upon the criterion used for defining the group and also upon the degree of thoroughness with which the work of the survey is carried out Again, the number will depend upon the representativeness of the population sampled and upon its age composition The standards of intellectual or social achievement applied to different age groups may not be consistent The same standards, moreover, may not apply with equal force to the two sexes Finally, the relatively high mortality rate of defectives must be taken into account O'Connor (1958) has surveyed some aspects of these problems

#### THE BRITISH ROYAL COMMISSION OF 1904

The first large-scale attempt to count the total number of mentally defective persons in any community was undertaken under the auspices of the British Royal Commission in 1904 Instructions were given to medical men in selected districts to visit schools, hospitals and institutions of all kinds and, further, to make enquiries of clergy, local medical practitioners, charity organizations and the police, with a view to ascertainment of all cases of defect The criteria of defect used in the survey were both educational and social The incidence in the general population, inferred from this investigation by Tredgold (1908), was 4.6 per thousand Since the patients were not compared with the numbers in the general population by age group, little can be gathered about the true frequency of defectives From the administrative point of view Tredgold's figure was valuable because it provided an estimate of the number of people likely to require special educational or institutional provision

## THE SURVEY OF 1929

A second survey of the incidence of mental defect in the general community in England and Wales was carried out by Lewis (1929) for the Departmental (Wood) Committee. The object, again, as with the Royal Commission of 1904, was to ascertain the extent of the problem to be dealt with from the point of view of the administrators of the Mental Deficiency Acts in force at that time and also of the Education Acts. Lewis had therefore to discover the frequency of all cases which were "potentially" certifiable or notifiable under either code. Imbeciles, idiots, feeble minded and the educationally and morally defective were included. A very detailed and complete survey was made in six districts which were representative samples of the whole community. The results can be briefly summarized by stating that 8.57 persons per thousand in the general population were found to be mentally defective. The contributions of the categories idiot, imbecile and feeble minded to this total were roughly in the ratio 5 : 20 : 75.

Some of the most significant points of the investigation remain concealed unless the age grouping of the ascertained cases is taken into account. Table III has been constructed from the figures given in the Wood Report. Although the totals indicate that the general incidence is 8.6 per thousand, there are remarkable fluctuations shown when age groups are separated.

TABLE III

INCIDENCE OF DEFECTIVES BY AGE GROUPS  
(Figures derived from Tables 2 and 17 of the Wood Report, 1929)

Age Group (years)	Population Sampled (in thousands)	Defectives Ascertained	Incidence (per thousand in population)
0-4	57	69	1.2
5-9	57	882	15.5
10-14	58	1486	25.6
15-19	57	617	10.8
20-29	102	860	8.4
30-39	91	515	5.7
40-49	82	441	5.4
50-59	60	294	4.9
60+	59	170	2.9
TOTAL	623	5334	8.6

The incidence represents a complex relationship between social and educational needs and the biological constitution of the population at each age. In early life defectives are difficult to ascertain except in extremely severe cases and, up to the age of 4 years, the child is not called upon to perform any duties of significance to the community. During the school period, however, intellectual deficit is brought sharply into the foreground. Between the ages of 10 and 14 accurately standardized tests can be applied to determine the degree of intellectual capacity. In this range the ascertainment, if so desired, can be done solely by psychometric tests. After the end of the school period the proportion of defectives suddenly drops because the rigid standards of scholastic environment no longer apply and there are more opportunities for adjustment by choosing suitable employment. Thereafter, as age advances, the continuous falling off of the incidence of ascertained defect may be due to lack of standardized tests for adults and to selective mortality favouring the normals. The peak of incidence occurs at the age of 12 years at this point it rises to 30 per thousand, or 3 per cent.

Lewis's estimates were made after careful examination of all children at school and the numbers of children in special schools or institutions would have, by themselves, provided much lower estimates. Some four-fifths of all the feeble minded children and even one quarter of the imbeciles and idiots were found to be attending ordinary school classes in the specified areas studied (see Table IV). Parents naturally oppose the transfer of their child to a school for the subnormal, if this can possibly be avoided, although the special school or centre may

TABLE IV  
ALL DEFECTIVE CHILDREN ASCERTAINED IN SPECIFIED AREAS  
(LEWIS 1929)

Imbecile or Idiot	Feeble-minded	Total	Location
131	1638	1769	Public elementary or private school
58	124	182	Special school
112	138	250	Institution
212	191	403	At home
513	2091	2604	All locations

provide the most suitable educational facilities. Moreover, backward children who are well behaved are often tolerated in ordinary classes and the stigma of deficiency is avoided.

#### COMPARISON WITH OTHER SURVEYS

Investigations in countries other than England have been made to determine the frequency of defectives. As might be expected, the results are not very consistent. Binet and Simon (1907) quoted the findings of a ministerial commission in France which reported 1 per cent of boys and 0.9 per cent of girls to be defective. They also mentioned that other authorities had given much higher estimates: Vaney suggested 2 to 4 per cent and Thamin and Abadie 5 per cent for the proportion of defective children of school age.

American estimates, for schoolchildren, usually have varied between 2 and 3 per cent. Naturally much depends upon definitions. As Yerkes (1921) pointed out, according to a current definition that any adult with a mental age of 12 years or less was defective, almost half the white males drafted into the American army in 1917 must have been defective. If, however, a mental age of 8 were taken as the limit, less than 2 per cent would fall into the defective group. Of the children entering school for the first time in Massachusetts, 2.6 per cent were considered, by Dayton (1939), to be defective and 11.2 per cent retarded though not defective. The Scottish Survey (1933) led to an opinion that more than 1.5 per cent, but not so many as 3 or 4 per cent, of schoolchildren were to be found in the mentally defective category. Dahlberg (1937) estimated that 3 per cent of boys and 1.7 per cent of girls in Sweden required education in special classes for the mentally defective. In the province of Milan, Casati (1959) found 1.1 per cent of the children oligophrenic and 3.1 per cent retarded.

#### DISTRIBUTION OF INTELLIGENCE TEST SCORES

So long as social valuation enters into the criterion of estimation there is little hope of obtaining incidence figures which can be of immediate scientific value. To a large extent, however, this objection is avoided by the use of standardized mental tests. The same test can be applied to different populations without prejudice. A limiting performance can be agreed upon

below which scores can be said to indicate defect. Naturally, the result of defining the group of mentally subnormal children in this manner will differ from the results of classifications based upon general behaviour.

One of the earliest studies on the distribution of test scores was made by Jaederholm in Stockholm. The figures, analysed by Pearson (1914), brought out clearly the fundamental nature of the problem. A group of children, considered to be feeble minded and on this account excluded from the ordinary public schools of the city, was examined with a modification of the Binet test. A sample of the total population of children was also available. Several important points became clear. First, it was shown that the distribution was continuous over the whole range of scores. There was no indication of a natural boundary between the normal and abnormal distributions. Secondly, if the diagnosis of defect had been made solely on the test scores

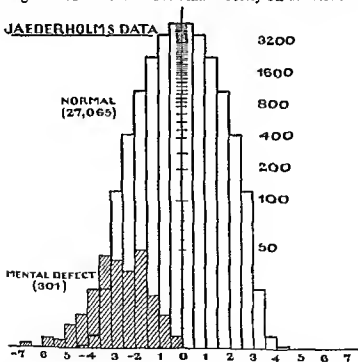


Figure 1 —Distribution of intelligence (Pearson, 1931)  
Estimate based on Binet test of 301 defective and 261 normal children  
(Standard deviation =  $\pm 1$ )

a somewhat different group would have been selected as abnormal from that which had actually been chosen. There was, indeed, a strong correlation between the criterion for defect and the test score, about  $+0.8$ . However, since the correspondence was not perfect, there was a large overlap between the test scores of the two classes. Finally, the distribution of intelligence scores in the general population approximates to the Gaussian or "normal" form. Thorndike (1925) made an extensive study on this point and on the whole he agreed with this conclusion. No very striking results follow from the observation, which merely indicates that the measurement of the character in question is determined by a multiplicity of small causes which can each act at random positively or negatively.

These findings are well illustrated by Pearson's (1931) diagram (Figure 1). The picture is similar to that obtained for measurements of stature in the general population. In both cases the main bulk of the population falls within the limits of twice the standard deviation. Mental dwarfs or, in the case of stature, physical dwarfs with measurements below these limits can be arbitrarily excluded from the normal population. Nevertheless, only a relatively small proportion of defectives, or dwarfs, have measurements so low as to indicate that they are certainly abnormal. The majority have measurements which still can be contained under a Gaussian curve fitted to the distribution of the normal population.

The work of Pearson thus first provided concrete evidence for the views put forward by Galton (1869) that intelligence in the general population was distributed in a continuous Gaussian curve. Galton had derived his assumption from the calculations made by the Belgian astronomer, Quetelet (1846), on the distributions of physical measurements in men. Galton further assumed that idiots and imbeciles were about equal in number to the eminently gifted, that is, each group amounting to about 250 per million. Unfortunately, even the contemporary figures for institutional defectives showed imbeciles and idiots to be ten times as numerous as this.

In samples of schoolchildren the lowest group is liable to suffer depletion by the absence of a proportion of defectives from the ordinary classes, so that the distribution curve which is obtained is inaccurate at its lower end. A large survey, covering

the whole of the school population in a specified area, by Duff and Thomson (1923) in Northumberland gave rise to a slightly asymmetrical frequency distribution. A complete survey (Matthews, Newlyn and Penrose 1937) of all the children of school age living in one small rural district gave rise to a similarly skewed distribution. In this district, 6 children out of 187, or 3.2 per cent, had scores deviating by more than twice the standard deviation below the normal value for the general population.

The distribution of Binet scores, expressed in terms of intelligence quotients, is usually found to be fairly symmetrical. This was demonstrated by Terman (1916) and has been confirmed more recently by Roberts, Norman and Griffiths (1938). A sample of 192 subjects from a survey made in an urban centre, embracing the complete child population of certain age groups was analysed. Roberts considered that the distribution of I.Q. was Gaussian, with mean almost 100 and standard deviation 15 points. The Gaussian nature of the distribution derived from a complete survey, using the Otis Group Test, was thought to extend as far as three and a half times the standard deviation below the mean. Quetelet (1846) had demonstrated that the distribution of stature followed Gaussian law to about the same limits.

If we choose to assume the reality of a Gaussian distribution for intelligence, we might decide that any score outside twice the standard deviation from the mean is to be considered exceptional. This enables us to define exactly how many children come into this class, that is to say, 2.27 per cent at either end of the scale. The standard deviation calculated for random samples of the child population by different observers varies from early estimates of 13 points (Terman 1916) and 12 points (Burt 1922) to larger estimates based on more comprehensive samples, such as the Scottish Survey (1933), of 16 to 17 points. Terman and Merrill (1937) gave 16 points as correct for the L and M revisions of the Binet test and, in the Scottish Survey, 1947, this test had a standard deviation of 19 to 20 points. However, Terman (1925) assumed that, for the Stanford Revision, the value was 15 points. If we then take the mean I.Q. of the population to be 100 and the standard deviation exactly 15 points, we can conveniently place the I.Q. below which the scores are to be considered exceptionally or abnormally low at 70, or



100—(2 × 15). Scores over 130 can be considered exceptionally high.

When tests are used which are not scored in terms of mental age, the I.Q. cannot be obtained directly. However, the scores of any test can be expressed in terms of the standard deviation calculated from a random sample. If so desired, the score of plus or minus one standard deviation can be arbitrarily defined

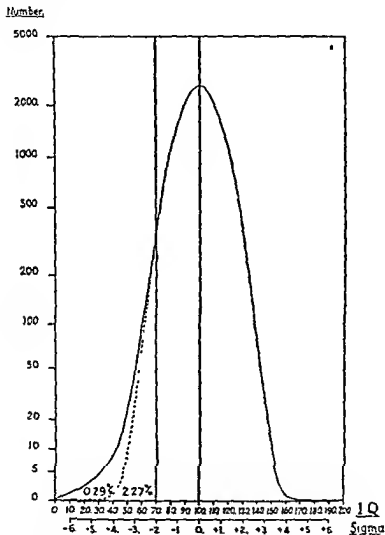


Figure 2. Theoretical distribution of intelligence test scores for the age group 10 to 14 years in the total population.

as equivalent to 15 points of I Q above or below 100. In this way, the I Q, preferably referred to as "mental ratio", could be defined, like the nautical mile, as a convenient constant unit of measurement. It would be correct when applied to Stanford Binet results and approximate for any other test of intelligence.

Two equivalent scales are shown in Figure 2. A curve giving the probable approximate distribution of Binet intelligence quotients in the general population, within the age group 10 to 14 years, has been drawn. The ordinate,  $y$ , is expressed in a logarithmic scale of the type  $\log(1+f) - y$ , where  $f$  is the frequency of each I Q value. The whole distribution is slightly skewed. If we remove a segment of the population, who score less than 70 or are beyond  $-2\sigma$ , we shall actually remove rather more than exactly the 2.27 per cent whose measurements would be included under a Gaussian distribution. The tail of the actual distribution based partly on estimates given by Lewis (1929) and partly upon I Q ratings for this age group, obtained by the Massachusetts Department of Health (see Appendix 4), extends to zero. A total population of 100,290 would include about 2560 cases below the 70 line. The Gaussian distribution in the figure covers 99.7 per cent of the total population leaving 290 outside its confines. Also the Gaussian population includes 2270 of the group who are, on the basis of test measurements, mentally defective. The curve shown in the figure is, of course, only one theoretical explanation. A single skewed curve might be found to cover the whole distribution accurately (see also page 50).

#### MALE AND FEMALE DISTRIBUTIONS

There is general agreement among different observers that the distribution of intelligence test scores for males is more widely scattered than it is for females. Terman (1925) showed that, on the Binet test, there were more boys than girls in the highest scoring groups of children. There appear also to be more males who have very low scores. The effect can be expressed succinctly by saying that the standard deviation of intelligence scores is usually found to be greater for boys than for girls. In the *Scottish Survey* (1933) the difference was 17 points to 16. Similar findings were reported by Duff and Thomson (1923), and Roberts, Norman and Griffiths (1945) stated

that boys were 13 per cent more variable than girls on intelligence tests. Results were obtained in the second Scottish Survey of 1947 which pointed in the same direction. Thus, if males and females are to be judged on the same scale, we shall expect to find a preponderance of male defectives in the extreme, or low grade, groups. In fact, most large surveys do show such a peculiarity. Lewis (1929) reported a high incidence in males, especially in the low grades, and the same excess was found in the Colchester institutional survey (Appendix 3).

The excess of male idiots and imbeciles is liable to be counter-balanced by a converse excess of mildly subnormal females, as in Pollock's (1926) data given in Appendix 4. It is difficult to be certain whether or not this effect represents a genuine biological difference between the sexes. The recognition of an excess of male institutional cases might be due to some form of social selection, e.g. if male cases are more difficult to look after at home than females. This view was supported by Wildenskov (1942), who found that 60 per cent of institutional cases in Denmark were males. The excess of females recognized to be mildly subnormal could also be due to a relative lack of social tolerance for women in this grade as compared with men. Furthermore, since intelligence tests are devised mainly by males, their content may favour the success of males at the top end of the scale. In spite of these possible sources of error it seems best to accept the data on their face value for the present and to assume that males are really rather more variable than females with respect to mental capacity. In the analogous case of stature, males show slightly more variation than females. As pointed out by Pearson (1897), this difference disappears if the greater average stature of males is taken into consideration and the coefficient of variation used instead of the absolute standard deviation. The same property is found for head measurements of adults. However, when we confine ourselves to absolute measurements, in all these characters the male is found to be the more variable sex.

#### INTELLIGENCE AND ITS MEASUREMENT

It is generally assumed that the tests devised and used by psychologists measure something closely allied to the criteria of social and scholastic efficiency by which we judge mental

defect Many psychologists prefer to be more definite and to assert that there is a quantity, "general intelligence", which can be estimated in every individual and that this quantity is the true index of mental defect, normality or mental superiority That is a convenient assumption Intelligence, as considered by Spearman (1927), is an abstraction like the idea of size Intelligence tests measure Spearman's "g" in the same way as a measurement of length, breadth or girth might be used to estimate an abstract quality of an object, which we could call its size The fact that we have a number of mental tests available, which are positively correlated with one another, only tells us that these tests have some property or properties in common Any three tests by themselves define a "g" of some sort With a larger number, the "g" cannot be precisely defined The assumption that we are actually measuring one thing, general intelligence, agrees reasonably well with the known facts about testing As Thomson (1939) has repeatedly pointed out, it is the simplest assumption to make, but it is not the only explanation and probably not the correct one The skill with which mental tasks are performed depends upon a large number of causes, some environmental and some hereditary In discussing general intelligence we must remember that its existence is only a convenient hypothesis The facts are the test scores To be precise, we should only speak of ability of each subject on a given test and not of his intelligence level

Observations made by Clarke and his co-workers (1954, 1958) have demonstrated that the scores on intelligence tests are greatly influenced by social environment in feeble-minded subjects Gains of 20 points in I Q are claimed to be not uncommon when favourable surroundings replace adverse conditions characterized by cruelty and neglect The question as to what tests give the best indication of mental qualities desirable in a civilized community is still unsolved Tizard, O'Connor and Crawford (1950) have analysed the different factors which are detected by intelligence tests in high grade patients and have shown the great variety of pattern found in different individuals The use of any one test is bound to lead to biased diagnosis An important commentary on this problem comes from the work of Tryon (1942) on the abilities of rats Although it is possible, by selective breeding, to produce strains of animals which are

specially gifted for one particular task, such hereditary abilities are markedly specific. Inherited ability to traverse one type of maze may not correlate at all with that required for another type

#### CULTURAL DIFFERENCES IN INTELLIGENCE

The concept of general intelligence tends to become strained when people with very different cultural backgrounds are compared. The now traditional idea, introduced by Blumenbach (Bendyske 1865), of separating mankind into constituent races each endowed with a particular set of mental qualities, has received little support from the findings of modern genetical research. Peculiarities affecting both mind and body, known to be determined genetically, are found to be distributed throughout all groups of mankind. The question of distinguishing races has been resolved into the identification of the same hereditary traits in different populations, the populations are then distinguished by the frequencies of these traits (Mourant 1954). The ABO series of inherited antigens shows marked gene frequency differences in populations all over the world, but the MN types are more evenly distributed. No qualities have been found to occur in every member of one racial group and in no member of another. The differences between races in respect of measurable qualities, such as stature and head size, are often found to be much less than might be commonly supposed. Morant (1939), for example, showed that differences between means of physical measurements among the so called European races were small and often statistically negligible. A full discussion of this question is to be found in the section by Barnicot in Harrison, Weiner, Tanner and Barnicot (1963).

Few people have attempted to justify Langdon Down's (1866) scheme for the ethnological classification of idiots. The clinical entity of "mongolism" was described, but it had nothing to do with racial Mongolians. Microcephalics were thought to be related to an Aztec race. A rather indefinite negroid type was included in the list, to which Davenport (1944) has drawn attention, and also a Malayan type.

A tendency sometimes has appeared in modern times to reverse the direction of Down's philosophy and to suggest that some racial groups are altogether less intelligent than others.

Porteus (1931), for example, found that Australian native adults were inferior to white or Asiatic children in test performances. Such field studies encounter great difficulties and require to be interpreted with caution. Marked discrepancies between scores on all kinds of tests have been found when white and coloured populations of the same country have been compared. The result, in the United States, is that proportionately far more coloured than white children could be classed as mentally defective. There is also more illiteracy among the coloured population and ability to do tests is strongly influenced by educational background. Analysis of the army intelligence tests (Yerkes 1921), applied to large numbers of males in 1917, showed that some racial or cultural groups were much more capable than others. For example, at every camp, the mean scores of whites were superior to those of negroes but a striking feature of the results was the large amount of overlapping in the distributions. Negroes from northern states, such as New York and Ohio, indeed, were superior to whites from the southern states, Georgia, Arkansas, Kentucky and Mississippi (Garrett 1945).

Even when culture is fairly homogeneous, as in Jamaica, Davenport and Steggerda (1930) found distinct differences between white, coloured and intermediate groups in the adult population. The selection of subjects was not random and the conclusions are open to criticism (Hogben 1931a). The coloured group however, was found to be definitely superior in mental arithmetic. The white group was superior in most verbal tests and in general knowledge. In tasks related to musical ability, coloured children and adults were at least equal to corresponding white subjects, though whites excelled at drawing. Interesting results have been obtained with American Indian children: the mean score of a group on Binet tests was much lower than that of Europeans of the same ages, but they did significantly better than European children on the Porteus maze test (Sparling 1941).

The Porteus test is less closely correlated with educational capacity and more strongly correlated with industrial capacity than the Binet (Berry and Porteus 1920). If some other test than the Binet, involving more "performance" and less scholastic knowledge, were used to pick out defectives, a group would

be selected whose personnel in the higher grades would be very different. The practical value of the scholastic type of test is mainly due to its use in estimating just those qualities which make adjustment in a highly industrialized civilization easy or difficult. Tests dependent upon special sense discrimination are not used for the diagnosis of defect, though it is possible to imagine a civilization in which the recognition of tunes or colours was as important as, say, arithmetic is to us. Some brilliant scholars are less capable of recognizing common tunes than are most imbeciles. No amount of intelligence can give a colour blind person the sensation of colour which he lacks physiologically. Useful appraisals of the value of tests in different populations and cultures have been given by Anastasi and Foley (1949) and by Klineberg (1935, 1951).

#### SENSE DEPRIVATION

People with sense deprivation are in some ways analogous to those whose cultural habits are foreign to the community. They must not be confounded with the intellectually defective. The ordinary intelligence tests do not function properly with deaf or blind subjects and it is often very difficult to estimate the I.Q. level. Such patients are sometimes more intelligent than they at first appear to be, a characteristic also found in some of those handicapped by paralysis from an early age. Performance tests can be used for deaf children with the blind verbal reasoning and memory tests are applicable (Hayes 1941).

The physically handicapped person needs, in general, to have a greater mental capacity than the physically normal in order to reach an equivalent level of social adaptation and usefulness. Pintner (1931) found that the average amount of scholastic retardation in congenitally deaf children was 2.3 years. Blindness also causes retardation, but usually in a lesser degree. The rare misfortune of blindness coupled with deafness necessitates a very high level of basic intelligence, both in the patient and the teacher, in order that successful relationship to the environment may be created. This has been demonstrated practically in the case of Helen Keller (1921) in the United States and in the U.S.S.R. in the case of Olga Skorokhodova (1947).

#### PHYSICAL MEASUREMENTS

If civilization depended solely on the physique of its popula-

tion, it would be perfectly reasonable to pick out socially incapable persons by physical measurements rather than by mental tests. On the whole, psychophysical tests show rather low correspondence with scholastic capacity. For example, Bagley (1900) found that quickness of motor reaction had a negative relationship to success in school. Sensitivity to pain, however, showed a positive correlation with intelligence. This observation agrees with the finding that some idiots, though by no means all, seem to take pleasure in hitting their heads or limbs against hard objects or even in having their teeth extracted. Strength of grip was found by Doll (1916) to be positively correlated with the intelligence level in defectives, to the extent of  $+0.62$  to  $+0.81$ , and the mean readings for his patients were lower than those for normals.

Stature and weight are also correlated positively with intelligence, though the relationship is not constant enough to be of much predictive value. The very extensive survey made by Goddard (1912) demonstrated that morons, imbeciles and, especially, idiots were all inferior to normals, both in mean stature and in mean weight, between the ages of 5 and 25 years. In the group of morons, however, there was extensive overlapping with the normals, and it is in this range that discriminative measurements might have been of greatest practical value. Pearson (1914) pointed out, after scrutinizing Norsworthy's data on 150 defective children, that as far as height and weight were concerned with the exception of one dwarf, all of the defectives might have been selected out of a group of normal children of adequate number.

Within the defective group body weight is a rather poor index of mental grade. Doll (1916) found the correlation for these two characters to be of the order of  $+0.3$ , and Ashby and Stewart (1933) gave a value of  $+0.24$ . Whiting (1915) found correlations of  $+0.324$  and  $+0.154$ , respectively, for mentality and weight and for mentality and height in criminals. Weight is a more comprehensive measurement of general body size than any linear measurement (Burt and Banks 1947), such as stature or sitting height, and it is of special clinical interest. Weight shows greater variation in defectives than among normals because of endocrine and nutritional disturbances and intercurrent diseases, which are more prevalent in defectives than in normals.



The weighing of patients is a routine procedure and the statistical information which arises from it has not been fully explored

#### HEAD SIZE AND BRAIN WEIGHT

It would be interesting and useful if it could be shown that a close relationship existed between head size and intelligence. The relatively large size of the brain in man as compared with other animals is mostly due to the greater development of man's cerebral cortex. It is probably to this accumulation of grey matter that he owes his superior intelligence. It is natural enough to enquire whether, within a given species, some relation may not hold between size of the head—which is largely determined by the size of the brain—and intelligence. In the case of man, males and females have to be classified separately otherwise we should start with the *a priori* fallacy that males, with their larger average size of head, were more intelligent than females. Similar reasoning has led some observers (Oliver 1932) to suppose, unjustifiably, that where the brains of negroes can be shown to be smaller than those of Europeans, the negroes must necessarily be mentally inferior.

Among homogeneous groups of schoolchildren, as well as university graduates, Pearson (1902) was able to demonstrate a weak, but positive and significant, relationship between head size and intelligence. The correlation coefficient varied between +0.097 and +0.139. A study by Estabrooks (1928), on groups of schoolchildren all aged 6, gave the result of correlating their scores in various intelligence tests with the cranial capacities, calculated from Lee's (1901) formula. They varied between +0.08 and +0.31 and were, on the whole, higher than those found by Pearson.

Among institutional defectives, investigations can easily be made by comparing intelligence level with head size in suitable age groups. Appendix I gives the distributions of cranial capacity, estimated by Lee's formula, in 440 male and 332 female adult patients. The relationship between intelligence and head size is weak but the correlation coefficient for the females is significant. A noticeable feature in both tables is the very wide variation of head size, especially in the lower ranges of I.Q. The average brain size falls off with diminishing mental

grade, but the variability increases. This effect probably applies both to brain weight and to head size. Sylvester (1961) found a skewed curve of distribution for brain weights of 157 males, mostly imbeciles and idiots: the mean was one sigma below that of a normal control sample and the variation was much increased. Large heads, found in idiots, are not always due to hydrocephaly, they can be associated with large histologically normal but functionless brains, as in megalencephaly (Apley and Symons 1947). Increased variability was also demonstrated in measurements of convolution width made by Ashby and Stewart (1935) on brains of 54 defective subjects as compared with 8 normals.

Furthermore, Ashby and Stewart (1933, 1934) took measurements of brain weight among other observations on defectives. The correlation for brain weight and mental age was found to be  $+0.15$ . It was pointed out that since body weight was significantly correlated with mental age ( $r = +0.24$ ) and closely correlated with brain size, the association might be attributed to the basic fact that defectives were as a rule smaller physically than normals. All mean measurements, in fact, diminish slightly with I.Q. until the imbecile level is passed and, below that, there is a sharp fall.

Although the mean value of head size for defectives in general is undoubtedly below the normal, the difference is insufficient for purposes of diagnosis. In the series of male institutional cases shown in Appendix 1, for example, the mean cranial capacity was 1402 c.c. with a standard deviation of 134 c.c. The mean is below the average for a group of 100 normal adult males from the same general population, namely, 1423 c.c., but here the standard deviation was only 89 c.c. This normal value is considerably lower than estimates given by Berry and Porteus (1920) for Australian males, but for those the standard deviation found was smaller, 79 c.c. The greatly increased variation in defectives makes prediction of intelligence from measurements of head size of little practical value. The extreme cases, hydrocephalics and microcephalics, will be obvious enough without recourse to measurement in most cases. Sometimes, however, it may be convenient for the clinician to be able to establish whether or not the head measurements of a supposedly defective infant are normal since mental tests at

ages below 5 years are not always reliable. For this reason, the figures for mean length, breadth and height of head, given by Berry and Porteus, are included in Appendix 2 (see also Table XXXI, p. 143).

#### GENERAL PHYSIQUE

Taken together as a group, the mentally defective are physically inferior to the rest of the population. It has yet to be determined how far this finding represents a genetical phenomenon and how far it is due to a variety of external causes, social, nutritional and clinical. The presence of definite diseases, hereditary or acquired, in a large proportion of recognized cases of mental defect, causes diminished vitality. Down's disease, mongolian imbecility, for example, carries a high mortality rate though, in consequence of improved medical care in recent years, its expectation of life has increased.

Analysis of routine physical examinations which had been carried out on 14,176 retarded schoolchildren was published by Dayton (1930b), and significant associations were found between the number of physical defects observed and the amount of individual mental retardation, both for males and females. Skin diseases, infestation and venereal disease were found with excessive frequency among mentally subnormal soldiers by Hodgson (1941).

Diseases cause intellectual defect directly if they attack the central nervous system. The amount of intellectual damage varies with the type of disease and with its severity. Williams (1926) listed 490 cases of neurological defects among children in schools for supposedly mentally normal cripples. The result, given in Table V, shows that mild degrees of mental retardation

TABLE V

CHILDREN IN SCHOOLS FOR CRIPPLES (490 CASES) (Williams 1926)

Clinical Diagnosis	Percentage at Each Intelligence Level			
	Above Average	Average	Below Average	Nearly Defective
Infantile paralysis	18.1	48.7	25.6	7.5
Infantile hemiplegia	8.8	32.4	30.9	27.9
Cerebral diplegia	0.0	15.1	24.2	60.6

are often found in such cases. A study of 167 feeble minded patients and 333 imbeciles or idiots, by Gordon, Norman and Berry (1933), showed that neurological abnormalities were to be found in many of the high grade cases and in most of the low grade cases. In the survey by Dawson and Conn (1931), encephalitis lethargica was found to diminish I Q in children. Conversely, children with rheumatic chorea showed no loss of intelligence as compared with the control population. A study of mental abilities in children with cerebral palsy by Schonell (1956) confirmed that I Q was reduced in proportion to the severity of neurological symptoms. In a group of 263 spastic children there were 98 hemiplegics with a mean I Q of 77.3, 85 paraplegics with a mean of 74.3 and 80 quadriplegics with a mean of 50.2.

Somatic diseases, which reduce general vitality, may affect the intellectual level indirectly, and so possibly may chronic malnutrition. The physical weakness associated with hookworm infestation has been shown by Smulhe and Spencer (1926) to have a very definitely deleterious effect on mental functioning. Perhaps the same is true for other parasitic diseases that are endemic in native populations. The actual loss in terms of I Q occasioned by physical diseases may not always be very great, e.g. a drop of 10 points, but if there is poor initial capacity the change may be sufficient to make just the difference between normality and subnormality.

#### STIGMATA OF DEGENERATION

Physique has been of traditional importance in the diagnosis of mental defect, particularly on account of the work of Lombroso (1887), who drew attention to what he termed 'stigmata of degeneration'. Malformations of the ears, hands and palate, as well as cranial deformities were considered characteristic of degenerate mental types, especially when they appeared to be simian. No satisfactory evidence for this view was brought forward. Degenerate ears, hands and palates are found among those in whom mental defect does not come under consideration. A type of corrugated scalp, for instance, has been labelled as a stigma of degeneration. Fischer (1922) and others expressed the opinion that the anomaly represents a reversion or regression to a lower form of life. The presumed

evidence for these assertions has been the reported presence of similar phenomena in certain African tribes, in animals and in defectives themselves. Among other objections to this concept is that a like condition has been noted in an otherwise normal person (Borrie 1953). Differences between normals and defectives can be expressed in terms of a difference in statistical frequency between the two groups. This difference is not as great as was formerly supposed. Channing and Wissler (1905) could find no significant deviation from the normal in the palatal structure of higher grade defectives and Burke (1931) found no distinction between idiots and imbeciles in respect of other stigmata.

There is a real concentration of physical peculiarities in some clinical types of cases, for example among mongols, microcephalics, gargoyles and subjects with endocrine disorder. In such conditions where there has been a gross disturbance of development many structures show dysplasias which can be attributed to retardation of growth at an early, critical period (Ford and Frumkin, 1942). Retardation of development can also account for the diminished size of defectives as a group. Dentition and puberty have also been found to be delayed (Davenport and Minogue 1930). An attempt to apply the Kretschmer system of typology has been made by Duis (1952) who explained that a large number of 'endogenous' cases were of the 'dysplastic' type. Careful sorting out of cases with endocrine defects, such as cretins and pituitary dwarfs, might make the issues clearer. Jaensch (1930) showed that the capillary structure of the nail bed is abnormal in defectives. These vessels are easily seen with a low powered microscope if a drop of oil is applied to the skin surface. The malformation however, may be an index of endocrine disturbance because it is specially noticeable in cretins. It also occurs in mongolism. Abnormalities of growth can also be occasioned by chronic disease associated with nutritional disturbance, either inborn or environmentally induced. Such signs are now recognized as stigmata of disease and not of degeneration.

#### DERMATOGLYPHS

The configurations of dermal sweat gland ridges on the palmar and plantar surfaces are sometimes known as dermato-

glyphs The arrangements of these structures are constant at all ages in the same person and they have been used from early times for purposes of identification They are useful in anthropological surveys because variations are to be found in different populations They also have significance as characteristic signs in certain clinical types of mental subnormality Dermatoglyphs were intensively studied by Galton (1892) who classified the finger tip patterns and showed that hereditary influences were determinants of their natural variety Methods of obtaining quantitative measurements of these patterns, arches, loops and whorls by counting ridges were devised by Bonnevie (1924)

Techniques of this kind have been used by Holt (1961) to investigate the distribution of these traits in families and clear evidence of genetical causation was obtained It is also known that the configurations of ridges on the palms are strongly influenced by heredity The comparative importance of environmental and genetical components in determining these characters has been estimated by studying them in identical twin pairs whose patterns usually show close similarity with slight quantitative differences

Special interest in dermatoglyphic traits with respect to the subject of mental deficiency first arose when Cummins (1936) demonstrated that the palmar patterns in mongolism were peculiar In almost all malformations which affect development of the arms and hands, some deviations from the normal pattern types are noticeable The retarded and ultimately defective growth of the limbs in mongolism is associated with a tendency towards transverse alignment of the palmar ridges Even grosser anomalies can be found in conditions involving such deformities as ectrodactyly and polydactyly In some cases of chromosomal aberrations very subtle distortions of the normal dermatoglyphs may be present As in the case of metrical traits like stature and head size, which have wide limits of normal variation, comparison of distributions of dermatoglyphic traits in defectives and unaffected controls shows much overlapping Large samples of data from the general population have to be obtained before valid diagnostic criteria can be set up Part of the deviation from the average pattern, which is found in some types of mental deficiency, may be controlled by the genes which produce normal variation The rest of the

deviation may be either environmental in origin or it may be connected with unavoidable morphological distortions which are consequences of the malformation itself

#### MENTAL DEFECT AND SOCIO-ECONOMIC STATUS

Since the estimate of defectiveness is closely allied to judgments of social competence, we may expect to find that I Q is positively correlated with social or occupational status. The coefficient of  $+0.28$  was given for this association by Duff and Thomson (1923), and that of  $+0.25$  by Gray and Moshinsky (1938). Burt (1926) estimated the mean intelligence of adults in the different occupational categories. These are shown in Table VI. Since the estimates of I Q are for adults, they must be accepted with reserve.

TABLE VI  
OCCUPATION AND INTELLIGENCE

Occupational Category	Average Intelligence Quotient (Burt 1926)
Higher professional administrative	153.2
Lower professional technical executive	132.4
Highly skilled clerical	117.1
Skilled	103.6
Semi skilled	97.5
Unskilled	86.8
Casual	81.6
Institutional	57.3

A common type of investigation is to test the abilities of children and then to classify them by the occupations or incomes of their parents. For example, Preda and Mates (1939) found a mean I Q of 115 for the children of parents with academic training, a mean of 105 for the children of parents in clerical occupations, 98 for the children of skilled workers and 91 for those of unskilled workers. Such results are sometimes used as an indirect method of arriving at the intelligence measurements of the previous generation on the assumption that intelligence level is in some way transmitted from parent to child. Material from different sources and obtained by the use of different tests tends to be very similar (Maxwell 1961). An example is given in Table VII. Figures like these are easily obtained and are of intrinsic interest, but do not prove that the classes of parents

listed necessarily have the same mean intelligence levels as the children. All observers agree, however, that children in the professional and clerical occupational groups are better at verbal and scholastic tests than are the children in the less

TABLE VII

SCORES OBTAINED BY A RANDOM SAMPLE OF URBAN CHILDREN ON THE PROGRESSIVE MATRICES PERCEPTUAL TEST (Penrose 1939e)

Paternal Occupation	Number of Children tested	Mean Chronological Age		Mean Score
		Years	Months	
Business owners	41	9	9	27.7
Professional	5	9	10	29.8
Highly skilled	29	10	2	28.0
Clerical and commercial	72	9	10	27.1
Skilled manual workers	277	9	10	24.2
Unskilled workers	217	9	11	21.6
Unknown	19	9	4	21.0
Total	660	9	10	24.0*

\* The standard deviation of the score for the whole group was approximately 12.7

skilled occupational groups. As shown by the results in Table VII, the same seems to be true for tests of non-verbal reasoning. An extension of this type of analysis into the range of mental

TABLE VIII

PATIENTS IN THE ROYAL EASTERN COUNTIES INSTITUTION (Penrose 1938)  
GRADE BY OCCUPATION OF FATHER

Paternal Occupation	Grade of Patient					
	Idiot (a)	Imbecile (b)	All Severe (a+b)	Feeble-minded (c)	Border line (d)	All Mild (c+d)
Directive Professional or Clerical	72	93	165	56	20	76
Skilled labour	60	126	186	108	50	158
Unskilled labour	83	186	269	242	93	335
Not known	5	28	33	42	16	58
Total	220	433	653	448	179	627



defect brings to light another phenomenon. Table VIII gives the distribution of defectives at the Royal Eastern Counties' Institution, Colchester, according to mental grade and occupation of father. Clearly the patients drawn from various social groups differ from one another in mental grade. The grouped technical occupations contribute twice as many patients of imbecile and idiot grade as borderline or feeble-minded patients. Unskilled labourers and men of unascertained occupation, including the fathers of illegitimate children, contribute more children of high grade defective types and fewer imbeciles and idiots. Economic, medical and biological factors probably combine to produce this pattern. In the higher income groups the borderline and high grade cases can often be given the kind of training and education they need outside institutions. Moreover, if the children of the more skilled fathers are, indeed, more intelligent than those of less skilled fathers, unskilled workers could be expected to have proportionately more feeble-minded children. The causes of severe defect may be more evenly distributed over the occupational grades.

A similar question arises in comparing urban and rural populations. Terman and Merrill (1937) found that the mean I.Q. of 1,964 urban children was 105.7 and that for 940 rural children 99.2. More subnormals were ascertained in rural than in urban areas, in proportion to population size, by Lewis (1929). The ratio of the incidence, urban to rural, was 6.7 to 10.4 per thousand inhabitants. The effect was attributed by Lewis to the migration of the more mentally able part of the population from the country to industrial towns. Investigations by Åkesson (1961) of a rural Swedish population showed again a high incidence of mental defect and tended to confirm that migration was an important factor in this.

#### MILITARY CRITERION OF DEFECT

According to the results of testing the personnel of the American army in the First World War (Yerkes 1921), a mental age of 8 years, corresponding to a Binet I.Q. of about 60, divides those who should be accepted for military duty from those who should be rejected. Men with mental test ages between 8 and 10 years were thought to be suitable for special labour battalions. However, the relationship of test score to

military efficiency was never clearly determined. Correlations between officers' ratings of military value and intelligence, as measured by tests, were low but varied from +0.5 to +0.23. Conscientious objectors to military service were found to be above the general level of intelligence (May 1920).

During the Second World War there was a great deal of testing of young adults in all English speaking countries, but the results were not made public to any large extent. It had been the general aim, of those who selected personnel for military duties, to exclude defectives though there were many differences of opinion about their usefulness. Anderson (1940) pointed out that defectives sometimes made more satisfactory naval ratings than their more intelligent brethren, provided that no psychopathic traits were present. Hecker, Plesset and Grana (1942) stated that, although the I.Q. of 60 or over is required to meet U.S. army induction standards, an I.Q. of 75, judged by the Binet or Kent test, should be the lower limit. Esher (1941) considered all cases below 7 years 11 months mental age untrainable. In a specially studied sample of 100 cases, referred for examination by the British army on account of supposed mental defect, he found that 80 per cent. had relatively high mental ages, i.e. from 9 to 11 years. The drop in intelligence test scores that normally occurs with advancing age was commented upon and Esher further recommended paying careful attention to school standards. Another side of the picture was demonstrated by Haskell and Strauss (1943), who examined the military service records of 100 mentally defective patients with a mean I.Q. of 70.7. After periods of service lasting some years, 31 had received promotion and only 12 had been discharged.

The brief Kent emergency test was used, in the U.S. army, by Atwell, Bloomberg and Wells (1941) and later it was replaced by batteries including non verbal elements. These writers stated that the basic reason for acceptance or rejection should not concern mental age, still less the intelligence quotient, but should be the subject's capacity in relation to army demands. Myers (1942) believed that intelligence tests for screening purposes should be preferably non verbal and supplemented by "job analysis".

It must not be assumed that mentally subnormal civilians

cannot adapt themselves to wartime strains. Benjacar (1940) reported that institutional cases co-operated well with air raid precaution work and useful constructional tasks. They showed no more liability to panic than normals and were very susceptible to efficient leadership; their reactions varied from blissful ignorance to moderately intelligent patriotic interest.

## CHAPTER III

### PRINCIPLES OF CLASSIFICATION

*Traditional Dichotomies—Pathological and Subcultural Defect—Medical Grouping of Cases in Hospital—Hospital Samples—Mental Defect and Biological Fitness—Fertility of Lower Grade Defectives—Fertility of Higher Grade Defectives—Fertility and Sex—Family Data on the Two Groups—Parental Consanguinity and Grade of Patient—Summary of Dichotomies*

#### TRADITIONAL DICHOTOMIES

It has been customary in medical treatises on mental deficiency to attempt to divide the patients into two classes. One traditional method was based upon separating "congenital" disease, with its origin before birth, from "acquired" disease, due to accidents which happen later. Shuttleworth (1895), for example, called defect due to cerebral abnormality, arising from formative or developmental defect, congenital. He referred to that which resulted from inflammatory or degenerative processes as non-congenital. Several uncertainties make this dichotomy unsatisfactory. First, it cannot be assumed that a disease or a degeneration, though it may have its onset in childhood or later life, has not its origin in prenatal events. Secondly, congenital does not imply hereditary, since the prenatal environment controlling development is not the same for all. Thirdly, injuries which occur during birth are difficult to ascribe to either class.

A more ambitious and more usual classification separates cases in which the origin is in the germ cells from those in which the origin is environmental. In other words, the classifier has to decide whether to blame nature or nurture. The terms "endogenous" and "exogenous" have had a very wide currency to indicate this opposition though other terms have usually been employed, in English text books, to indicate the same things. Thus, Ireland (1877) used "genetous" to signify hereditary causation and defined acquired disease by specification,

e.g. hydrocephalic, epileptic, paralytic. The words "primary" or "secondary" were introduced by Tredgold (1908) to signify respectively the product of an impaired germ cell or environmentally arrested development of a potentially normal brain. The substitution of new terminology did not remove fundamental inaccuracies, it rather tended to perpetuate them. The difficulty obscured here is that, in a large proportion of cases, as Wildenskov (1934) has pointed out, both hereditary and acquired factors combine in producing the end result of mental defect. For a biologist it is merely a platitude to state that the condition of a living organism at any time is the product both of its nature and its nurture. It is also obvious to a mechanic that the performance of an engine at any time, under given conditions, depends both upon how efficiently it has been constructed and how carefully it has been handled. Medical methodology, however, for reasons which are excellent in clinical practice, repudiates the simultaneous diagnosis of more than one disease. If mental defect is the condition in question, the physician is obliged to diagnose it either as some hereditary or as some acquired disease. The method is not very inaccurate when we are concerned only with severe cases, idiots or imbeciles. It fails badly in the analysis of milder cases, where social adjustment is decisive in determining whether or not the patient is to be classified as intellectually subnormal.

#### **PATHOLOGICAL AND SUBCULTURAL DEFECT**

A fresh approach to the problem of clinical classification was made by Lewis (1933), who suggested the division of defectives into "pathological" and "subcultural" classes. The term "physiological" would be more natural than "subcultural", but it has been used in too limited a sense, for example by Juda (1936), to indicate only borderline cases. Among recognized cases of mental defect we find a certain number suffering from *definite physical diseases or pathological conditions*, which interfere with the functioning of the brain in one way or another. There is no doubt that a very large proportion of idiots and imbeciles are correctly described as "pathological" in the ordinary sense of being diseased. Neuropathological studies have demonstrated that the *overwhelming* majority of the brains of low-grade defectives, examined at post mortem, show

structural abnormalities (Crome, 1960) It is immaterial whether or not the diseases in question are due to environment or to heredity Lewis himself, however, tentatively suggested that the majority of cases of pathological defect were environmental in origin

There is statistical support for Lewis's classification if we assume that the distribution of ability on intelligence tests, in a normal human population, should be Gaussian Far too many individuals exist, whose abilities are more than three or four times the standard deviation below the normal mean to be fitted under a Gaussian curve (see Table IX) The IQ levels here are those in Table I and the percentages agree with those

TABLE IX

LOWER LIMITS OF THE DISTRIBUTION OF INTELLIGENCE IN THE GENERAL POPULATION (AGE GROUP 10-14 YEARS)

Percentage Distributions	Idiot	Imbecile	Feeble minded	Total
Observed Defectives	0 06	0 24	2 26	2 56
Normal Gaussian prediction	0 00	0 04	2 23	2 27

assumed in Figure 2 A slightly different analysis, leading to similar conclusions, has been made by Dingman and Tarjan (1960) using a standard deviation for IQ of 16 points If the standard deviation of IQ were 15 points, only one imbecile in 6 and one idiot in 10 000 could belong to the normal population For the feeble minded, the position is different and, on the basis of intelligence tests alone, the great majority of them might be regarded as members of the normal population Diminished intellectual capacity of relatively mild degree can be interpreted as failure to meet the demands of local culture Hence, the term "subcultural" can be applied to most of the feeble minded, though few imbeciles or idiots can be reasonably included in this category

#### MEDICAL GROUPING OF CASES IN HOSPITAL

Lewis's dichotomy, though the best so far devised, is difficult to apply in clinical medical practice, particularly in so far as

actual institutional cases are concerned. Those cases, in which a chronic neurological abnormality or a developmental deformity is observed, can be separated clinically from the rest, but sometimes no known disease can be identified. It is never certain, then, that examination using new knowledge could not have detected significant anomalies. A residue always remains of undiagnosed defectives who cannot be certainly distinguished from subcultural or physiological defectives. For example, in the Colchester Survey (1938) of 1,280 patients, 308, or 24·0 per cent, showed no definite clinical abnormalities such as might be supposed to indicate pathological conditions underlying the defective mental state (see Table X). These 308 patients were relegated to a residual group which would contain nearly all the subcultural cases as defined by Lewis. In a somewhat similar survey, Halperin (1945) found that 45 per cent of the cases had no relevant clinical manifestations but, as in most American institutional samples of defectives, epileptics were excluded. In a classification of defectives recommended for use in the United States, there is an "undifferentiated" class. This has not quite the same connotation as residual or acinical, since instances of "familial" defect are excluded. However, the

TABLE X

EXAMPLES OF MEDICAL GROUPING OF CASES IN HOSPITAL

Grade	Total Number of cases	Clinical Group		Residual Group	
		Number	Percentage	Number	Percentage
Borderline	179	145	81 0	34	19 0
Feeble-minded .	448	284	63 3	164	36 7
Imbecile .	433	340	78 5	93	21 5
Idiot .	220	203	92 3	17	7 7
Total .	1280	972	76 0	308	24 0

group is a large one and it comprised, for example, 2,137 out of 5,238 Massachusetts certified defectives in 1939.

Among the idiots in the Colchester Survey, 7·7 per cent had no clinical abnormality, though, of course, modern methods of diagnosis might have revealed unexpected pathological processes. Among the imbeciles, 21·5 per cent were left in the

residual group and, among the feeble-minded, 36.7 per cent. Of the borderline patients, however, fewer were without clinical signs of abnormality, because most of them (98 out of 179) were epileptic or psychopathic, otherwise they would not have required care, supervision and control. The same consideration applied in a lesser degree to the feeble-minded.

It is not quite clear how far the term "pathological defect" was originally intended to cover psychoses, epilepsy, psychopathy, delinquency and so on, but something more than mere subcultural defect is needed to justify institutional supervision of high grade cases. If "subcultural" and "pathological" are to be exclusive terms, most patients under supervision have pathological defect in the sense that, mentally or physically, they suffer from some chronic illness. In the great majority of recognized cases of mental defect the interplay of causal factors leading to eventual admission to hospital is so complex that an exclusive categorization can be only an approximation.

Many of the cases in the clinical group are known to have diseases attributable to single causes. These may be harmful genes, aberrant chromosomes or environmental accidents. In such cases, it can be assumed that the subject would have had normal intelligence in the absence of disease. Whether the level of ability would have been high or low is a matter of indifference in relation to diagnosis. This principle applies to most of the severe cases and particularly to idiots.

Among the feeble-minded and borderline cases it is otherwise. It is rarely possible to specify only one cause of social failure and the potential mental level, even in the absence of disease, is the chief factor of importance. The majority of feeble-minded defectives are not far removed from the average and they are accepted as part of the normal population. They are liable to require care, supervision and control under conditions of social or economic stress. Disabling illness or lack of training, coexisting with subcultural mentality, merely increases their likelihood of recognition. In borderline cases the intellectual defect is, by itself, even less indication for institutional supervision. Additional factors, causing social incompetence, must be present if care and control are necessary for such people.



## HOSPITAL SAMPLES

Defectives who are cared for in institutions or hospitals fall naturally into two main groups if they are classified objectively by the severity of their mental retardation. One group contains idiots and low grade imbeciles, with disabilities due to disease or malformation, whose mental capacities would be normal in the absence of disease. A considerable proportion of all cases of severe subnormality in the community have to be cared for in hospitals. In England this proportion is about one quarter. The other group contains mild cases, feeble minded and borderline patients with subcultural intellects and also high grade imbeciles. Usually the intellectual defect in members of this group is not pronounced enough to have prevented some adaptation to society in the absence of additional extraneous factors. These factors can be physical or mental infirmities which require medical treatment. Occasionally, institutional training is needed to counteract antisocial influences in a patient's home. Only a very small fraction of all those in the general population with subcultural intellects are actually con-

NUMBER OF CASES

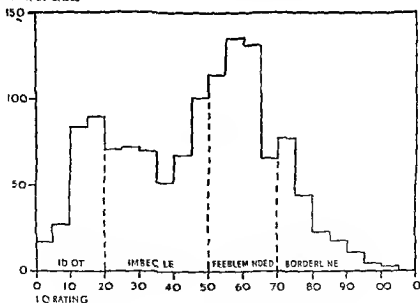


Figure 3 —Hospital sample (see Appendix 3)

sidered defective in the medical sense so that they require training in hospital. The proportion of them actually under hospital supervision at any given time in England and Wales is less than 3 per cent.

The therapeutic requirements of these two groups are somewhat different and hospitals are occasionally staffed to deal only with one or other type. In practice, it can be efficient and economical to treat both in the same hospital. In the Colchester Survey the two groups could be differentiated, irrespective of age grouping, by intelligence level as measured by the Binet I Q. The distribution shown in Figure 3 has a natural dividing line at about I Q 37, or, for adults, at a mental age of a little over 5 years. The severely affected cases with I Q of 0 to 39, moreover, were considerably younger than those with I Q 40 and above. The most frequent age range for the low grade group was 10 to 14 years whereas the most frequent age range for the high grade group was 25 to 29 years. The sex incidence was also different in the two groups, in that males predominated greatly among the severely affected. The complete table, showing the distributions of patients by I Q, age and sex, is given in Appendix 3. The statistics of institutional cases given by Dayton (1939) show the same general trend (see Appendix 4), for there is a sudden "jump" in numbers between the I Q group 30 to 39 and 40 to 49.

It is improbable that there is any natural demarcation between the two institutional groups in the population as a whole. As shown in Table XI, a disproportionately large number of imbeciles, in a sample area, were not in any institution but were cared for under statutory supervision or guardianship. The

TABLE XI

LOCATION OF ASCERTAINED CASES OF MENTAL DEFECT IN AN AREA  
SERVED BY A LARGE HOSPITAL IN JULY 1933

	Idiot	Imbecile	Feeble minded	Total	Males	Females
Number in Hospital	31	94	83	213	124	89
Number under Statutory Supervision or Guardianship	30	149	47	226	90	136

predominance of males in the institutional sample suggests that they are not tolerated as well as females are at home

In a hospital, which supplies nursing and training facilities, those who need care and supervision have the most urgent claims on admission. The idiots need nursing on account of their helplessness and the feeble-minded need psychiatric supervision on account of their propensities for maladjustment in the community. Between these classes is a group, mainly composed of imbeciles, who are too low grade to be problems in the community and yet are capable of looking after themselves to some extent in the sheltered environments of their own homes, the homes of foster parents or of guardians.

#### MENTAL DEFECT AND BIOLOGICAL FITNESS

The type of social failure to which mental defect is equivalent is, as we have seen, closely allied to educational failure. The prevalence of associated disease in patients indicates another cause of social failure, namely, that from the point of view of physical health. Closely related to individual physical unfitness is biological unfitness, and we may ask how far defectives are biological failures. The ultimate test of biological fitness is ability to reproduce. Failure to reproduce may be due to ambient conditions which include disease, injury or accident. It may also be the result of genetical constitution. Natural selection determines which genes are carried on to future generations and which are not. The perpetuation of a gene depends upon how many offspring are produced by each individual who carries it. In estimating fertility, the fitness of the offspring themselves is not taken into consideration. If a gene confers biological success, in this sense, which is greater than the average level for the species, the prevalence of a gene can increase. Conversely, if the possessor of a gene tends to have diminished fertility, this gene will gradually die out unless replaced by fresh mutations.

The effective fertility of an individual can be interfered with at various levels. The embryo may fail to develop or its internal harmony may be so disturbed that it fails to survive early life. Genes which cause such disturbances of development are termed "lethal" or "sublethal", and the abnormal individuals are necessarily infertile. Anencephaly is a lethal condition in

man and so also is infantile amaurotic idiocy. No affected subjects can have children of their own. Less severe diseases or disabilities can cause partial loss of fertility, which may sometimes be socially conditioned as, for example, in congenital paralysis, blindness or deaf mutism. In the case of such a disease as haemophilia, diminished fertility is typically caused by early death from haemorrhage. As far as mental defect is concerned, low grade cases are mostly unable to reproduce at all and by this biological criterion they can be differentiated from most high grade cases.

#### FERTILITY OF LOWER GRADE DEFECTIVES

Among idiots there is almost complete absence of effective fertility, for reasons which are usually both physical and social. With imbeciles, fecundity is possible but rare. Thus, among the parents of defective patients of all types, only a very small number are of imbecile grade. In the Colchester Survey for example only four imbeciles and no idiots were discovered among the parents of 1,280 cases. Also, no idiots in the sample of patients had children of their own and only 7 out of 138 female imbeciles over the age of 16 (with a mean age of about 29 years) had offspring. These 7 imbeciles had, on the average, two pregnancies each and about half of the offspring might have been expected to reach maturity. The actual fertility of imbeciles in the general population is probably even lower than this sample would suggest, since pregnancy in a defective is an important determining factor leading to institutional care.

Roughly, the lower limit of mental grade compatible with reproductive activity seems to correspond with the division between the two classes of institutional defectives already described and rests at an IQ between 35 and 39 points. The decisive factors are physical development, general appearance and social opportunity but ability on the Binet test is a rough guide. Menstruation occurs in female idiots unless sexual development or the endocrine system is grossly disturbed. Hence, fertility among them is a possibility. Danenhower (1948) found no appreciable abnormality in menarche, periodicity and menopause in a sample of defective females of all grades. The fact that idiots are not fertile is probably due as much to psychological as to physiological circumstances, in that they

do not attract mates. A male idiot is even more handicapped in this respect than a female. The same applies to males of imbecile grade for effective fertility in male imbeciles is much rarer than it is in female imbeciles.

#### FERTILITY OF HIGHER GRADE DEFECTIVES

The question of fertility among the feeble minded has been the cause of much speculation and is still unsettled. In so far as the milder types of defectives can be considered members of the general population, it may be expected that they will share in the differential fertility which has been shown to be present when occupational groups are examined. The occupational groups with the highest birth rate are among the least skilled, members of the professional and highly skilled groups have fewer children (Carr-Saunders and Jones 1937). People with Binet I Q of 70 or thereabouts are only capable of unskilled labour or even casual labour and, therefore, belong to a high fertility stratum.

In assessing the degree of fertility of the feeble minded, two points need special consideration. First, some feeble minded parents may have families which are large as compared with those of parents with normal intelligence, but the total contribution to the next generation depends also upon those who have no children. The total contribution may not actually be as great as the finding of a few large families with feeble minded parents would suggest. Secondly, biological effects of increased fertility can best be measured when families are followed up for the period of a whole generation. Thus, if the children of defectives should be physically weakly as compared with the rest of the population, the genes inherited from their parents will not be favoured even though the families they come from are large. On these points it is difficult to obtain exact information but some facts are suggestive. In a survey, made by the Departmental (Brock) Committee on Sterilization (1934), on the offspring of people notified as mentally defective, the proportion of children who died under the age of one year was about double that for the general population.

Since severe defect is associated with infertility, a break must come somewhere in the line of increasing average size of family with diminishing intelligence. Is the change sudden or gradual?

There are some reasons for supposing it to be gradual. For example, Jones (1934) in his survey of the general population of the Merseyside found that fertility, measured by the mean size of family, in the very lowest social grade was less than that in the grade immediately above it. Studying the parents and grandparents of defectives in the Colchester sample and classifying them by mental grades led to the conclusion, demonstrated in Table XII, that the greatest fertility occurred when parents had a mean I Q of about 80 or 90 points. When parental grade was below this, the families were smaller.

TABLE XII  
RELATIVES OF DEFECTIVES, (Colchester Survey 1938)

Approximate I Q of each Grandparent	Number of Cases	Mean Number of Uncles and Aunts per patient (Registered Births)*
122 and 100	6	5.17
100 and 100	1663	6.22
100 and 78	55	6.47
100 and 56 or 78 and 78	17	7.35
78 and 56	3	6.00
56 and 56	5	4.80
Approximate I Q of each Parent	Number of Cases	Mean Number of Sibs per Patient (Registered Births)*
122 and 100	9	2.89
100 and 100	797	4.72
100 and 78	196	5.45
100 and 56 or 78 and 78	113	4.52
100 and 34 or 78 and 56	54	3.82
78 and 34 or 56 and 56	24	3.58

\* These means cannot be directly compared with means obtained for the general population because the families are all selected by the presence of at least one child and therefore are too large. They can be rightly compared with one another.

#### FERTILITY AND SEX

A difference in fertility between males and females has been observed among the milder cases of defect. In numerous surveys defective mothers have been ascertained more frequently than defective fathers. This phenomenon was observed and recorded by Rosanoff (1931), Halperin (1945) and in the Brock Report (1934) on very different types of material. It also appeared in

the Colchester Survey where three times as many mothers as fathers of patients (i.e. 12 per cent against 4 per cent) were considered to be subnormal mentally. These findings agree also with what is known of the biology of specific conditions causing severe defect, like mongolism where eleven examples of fertile females are known but none of fertile males. Jervis (1939) reported three phenylketonuric females who had offspring but no actually fertile males are on record. One partial explanation is that there are more female than male defectives within the fertile range. Another cause might be the impossibility of ascertaining defective fathers whose offspring are illegitimate. Furthermore, since care of the child depends more upon the mother than upon the father, a defective mother is more likely to be noticed by social workers than a defective father. While these factors may partly explain the difference, psychological and cultural circumstances must also be taken into account. The initiative in sexual approach, as well as in the economics of the family, belongs chiefly to the male. Hence, low mental capacity is a more serious biological handicap to a male than it is to a female.

Certain anomalies dependent upon sex chromosome aberrations are associated both with mental subnormality and lowered fertility. Spermatogenesis is absent in a Klinefelter male. Primary ovarian agenesis occurs in females with Turner's syndrome but such patients are rarely retarded mentally. So-called "superfemales" with increased X chromosome complement have diminished fertility and are mildly mentally subnormal (see Chapter IX).

#### FAMILY DATA ON THE TWO GROUPS

As already indicated in the previous chapter and demonstrated in Table VIII, family history investigation of higher grade cases leads to different results from that of lower grade cases. An inverse relationship holds between occupational levels of father, home conditions as judged by cleanliness, size and comfort, and the mental levels of patients. If feeble-minded and borderline patients are separated from idiots and imbeciles, it is found that, in the first group, home conditions are, on the average, inferior and, in the second or low grade group, they are probably distributed as in the general population.

Table XIII shows the results obtained in the Colchester Survey after the homes of 1,013 patients had been visited and rated by social workers

TABLE XIII

PERCENTAGE DISTRIBUTIONS OF RATINGS OF HOMES OF DEFECTIVES

Rating of Home Conditions	Imbecile or Idiot (531 cases)*	Feeble minded or Borderline (482 cases)*	Fictitious General Population
A Very Good	4.9	0.6	5
B Above average	21.7	10.4	20
C Average	49.7	44.2	50
D Below average	18.8	34.6	20
E Very bad	4.9	10.2	5

\* 122 imbeciles and idiots and 145 feeble-minded patients were homeless

Closely parallel to the occupation and social findings in the patients' families are the actual assessments of intelligence on relatives. In the Colchester Survey again 12.1 per cent of the parents of 448 feeble minded cases were considered to be themselves feeble minded or imbecile whereas only 6.5 per cent of the parents of imbeciles and only 2.7 per cent of the parents of idiots could be placed in the defective category (Appendix 10).

Comparison of mental grades of parents in two main groups of patients, mild and severe, is shown in Table XIV. Mental subnormality is more noticeable among parents of the higher grade patients. The same applies, in a lesser degree, to grandparents. With respect to sibs, the situation, as shown in the same table, is a little more complex. If defect occurs among the sibs of any patient, it tends to be of the same degree as that in the patient. However, the sibs not classified as defective or retarded are usually found to be brighter when the patient has severe defect than when the patient has mild defect. Actual testing with the Stanford Binet confirms these results, as described in Chapter VI. Similar considerations, in an attenuated form, apply to uncles, aunts, cousins and more distant relatives.

These family history peculiarities have been found for severe and mild cases by observers in many different countries, for example, by Lewis (1933), Wildenskov (1934), Halperin



TABLE XIV

NUMBER OF PARENTS AND SIBS IN DIFFERENT MENTAL GRADES  
(Colchester Survey, 1938)

Mental Grades of Parents	Grade of Patient		Total (1280 cases)
	Imbecile or Idiot (653 cases)	Borderline or Feeble-minded (627 cases)	
Superior . . .	7	4	11
Average . . .	1073	835	1908
Borderline or Feeble-minded	196	346	542
Imbecile or Idiot . .	1	3	4
Unascertained . . .	29	66	95
Total . . .	1306	1254	2560

Mental Grades of Sibs	Grade of Patient		Total (1280 cases)
	Imbecile or Idiot (653 cases)	Borderline or Feeble-minded (627 cases)	
Superior . . .	40	28	68
Average . . .	1968	1677	3645
Borderline or Feeble-minded	312	453	765
Imbecile or Idiot	109	58	167
Unascertained	120	105	225
Total . . .	2549	2321	4870

(1946) and by Roberts (1947, 1952). However, Brugger (1941) held that the decisive differentiating factor was not the grade of the patient but the clinical type of the case. Undoubtedly there is much overlapping of the concepts of low and high grade defect, of the subcultural and pathological concepts and the residual and clinical concepts; the dichotomies produced by them are not coextensive. The biological concept of fertility seems, however, capable of clearing away some of the confusion. The possible causation of severe defect is subject to the restriction that severe defect can scarcely ever be transmitted from parent to child and this restriction does not apply to the causation of high grade defect.

#### PARENTAL CONSANGUINITY AND GRADE OF PATIENT

The high incidence of blood relationship between father and

mother of a defective patient has often excited comment. The results of some early surveys were analysed by George Darwin (1875). Estimates of the incidence of defective patients with first cousin parents ranged from 2.9 per cent to 3.8 per cent. Later, Shuttleworth (1886) calculated that 2.9 per cent of the defectives at the Royal Albert Institution had first cousin parents and that, altogether, 5 per cent had parents who were in one degree or another consanguineous. The incidence of cousin marriages of all degrees in a control population of general hospital patients was only 0.8 per cent (Bell, 1940). There has been a gradual reduction in the number of cousin marriages during the last 50 years but, even when this decline is allowed for, the figures for parents of defectives are phenomenally high. Among 800 consecutive admissions of low grade children to the Fountain Hospital, London, from 1949 to 1960, 1.3 per cent had first cousin parents, the control figure for children admitted to general hospitals would be 0.4 per cent (Berg, 1962h).

Cousin parents of all degrees are more commonly found for low grade than for high grade patients. Combining the figures from the Colchester Survey with those from a survey made by Duff and Dingee (1941) at Orillia, Canada, led to the result shown in Table XV. The total consanguinity rate is very high, more than twice that in the general populations from which the cases were drawn. Incest and other illegal unions are

TABLE XV

PARENTAL CONSANGUINITY INSTITUTIONAL CASES  
(Penrose 1938, Duff and Dingee 1941)

Degree of Parental Relationship	Cases with Related Parents			
	Imbecile and Idiot		Borderline and Feeble minded	
	Number	Percentage	Number	Percentage
Illegal unions incest	6	0.3	10	0.9
Cousins of all types	63	3.0	26	2.2
All types of consanguinity	69	3.3	36	3.1
Total number of patients surveyed	2190	100.0	1172	100.0

remarkably frequent among parents of high grade cases, this is partly due to the preferential selection, for institutional care, of illegitimate children whose parents are of subcultural mental level. With regard to the legitimate cousin marriages, the position is reversed. These are more numerous (3.0 per cent) among the parents of low grade cases (especially idiots) than among the parents of high grade defectives (2.2 per cent). As will be explained, in Chapter IV, this strongly suggests that, among the idiots, there are to be found rare, recessively inherited conditions. Though recessive inheritance is characteristic of many kinds of low grade defect, it is not true, as Goddard (1914) originally suggested, that all or even a large proportion of defectives are examples of just one recessive type.

#### SUMMARY OF DICHOTOMIES

Descriptions of the two classes into which defectives can be roughly divided are summarized in Table XVI. The two main groups of cases can be termed "severe" and "mild", but, as previously pointed out, the qualities that are listed as characteristic of the two types of cases are not specific and there is a great deal of overlapping. Nor are the properties listed in this table intended to be exhaustive. It may, however, be useful to consider the problem of defect within this framework, because the essential difference between the two groups can be expressed in terms of biological fitness. In consequence of this, the genetical causes in the two groups are necessarily different. Several types of idiocy are recessively inherited and typically the disposition can be transmitted by normal parents. Among the mild, fertile group, there is no such restriction on genetical causes, genes causing dominant traits may be factors through more than one generation. The lack of any marked distinction between the cases of mild defect and members of the general population makes it reasonable to assume that the same *genetical mechanisms which produce variations in intelligence* in the general population will be determining factors in the production of mild defects. Genetical factors, like those which cause normal variations in stature, are certainly multiple and probably additive in their effects.

The frequencies in the two groups are characteristic. Severe cases are comparatively uncommon and the events which

TABLE XVI

THE TWO MAIN GROUPS OF THE MENTALLY SUBNORMAL WHO REQUIRE HOSPITAL CARE

Degree of defect	Severe	Mild
Incidence of group in population	Uncommon $\frac{1}{4}$ per cent	Common 2 per cent
Proportion of group in hospital	Many 25 per cent	Few 3 per cent
Sex incidence	Males predominate	Females predominate
Psychological classification	Low grade imbecile or idiot (modal I Q about 17)	High grade simpleton moron feeble minded (modal I Q about 57)
Predominant medical classification	Pathological clinical associated with physical malformations	Physiological achinal residual associated with behaviour disorders
Mental capacity in absence of disease	Normal	Subcultural
Physical measurements	Means below normal in creased variabilities	Means and variabilities within normal range
Biological classification	Non fertile	Fertility usually normal
Traditional obsolete view on causation	Environmental secondary exogenous extrinsic	Hereditary primary endogenous intrinsic
Status of relatives	Parents rarely defective brothers and sisters occasionally defective and sharply distinguished from normals	Parents brothers and sisters rather frequently defective but not sharply distinguished from normals
Typical hereditary causes	Rare specific genes autosomal aberrations	Common genes multiple additive genes sex chromosomal aberrations
Typical environmental causes	Pre natal maternal influences cerebral disease or injury in very early life	Deprivation cerebral disease or injury in childhood antisocial environment
Treatment	Elementary training nursing correction of biochemical errors cerebral surgery	Special education socialization physical training psychotherapy

produce them tend to be relatively rare accidents, rare diseases or rare genetical processes. Conversely, mild cases are common and most causes of disability here are ordinary events either environmental or genetical.

The separation of cases into these two classes is natural also from the point of view of education and therapeutic objectives. The mild cases require social training and special education so that they may be, as far as possible, returned to the community as useful citizens. They may require medical treatment, an

essential part of which is often psychiatric. The severe cases present a different problem, they cannot be expected to take any useful part in the affairs of the community, except under supervision. Moreover, the lowest grades are permanent invalids requiring continual nursing care and the usual aim is little more than to make them as healthy and as comfortable as possible.

## CHAPTER IV

### PROBLEMS OF CAUSATION

*Nature and Nurture—Hereditary Material—Mutations—Germ Plasm Injury—Anticipation—Gene Mutation and Selection—Dominant Characters—Rare Recessive Characters—Incompletely Recessive Characters—Sex linked Genes—Inheritance of Chromosome Aberrations—Maternal Genetical Influences—Maternal Environmental Influences—Intranatal Environment—Postnatal Environment—Methods of Distinguishing between Nature and Nurture—Intelligence of Twin Pairs—Evidence from Children in Foster Homes*

#### NATURE AND NURTURE

As every living organism is the product both of hereditary and environmental influences, the problem of finding a cause for any given peculiarity resolves itself into an examination of both types of agency. An influence which acts equally upon all individuals in a species or which is common though not universal cannot be blamed exclusively for a rare deviation. We may suppose, however, that an unusual concatenation of common agencies can cause rare peculiarities. In human genetics the principle of looking for rare agencies as the causes of rare diseases is quite important. Of necessity, most common variations are not very harmful. Conversely, genes responsible for hereditary diseases are also, of necessity, relatively rare. If this were not so the species would be very unstable. Thus, in speaking of specific causes of mental defects we shall in the main, be thinking of rare events.

The distinction between causes, which are said to be hereditary or part of the individual's nature and those which are environmental or pertaining to nurture, must be based upon temporal sequence. Consider, for example, a machine such as a watch. Certain metallic alloys and other substances are prepared and out of them the wheels, spindles and framework are fashioned. They are then assembled and adjusted before the watch is ready for use. After this, the watch is expected to go

for a long time provided that it is wound up regularly and not dropped on the floor or allowed to get damp or full of dust. Eventually the bearings get worn down or a part breaks. If it should fail to work, say on account of a broken spindle, the cause may be attributed to faulty materials, faulty machining or construction or to misuse, by specifying the chief unusual circumstance which is connected with the accident. We might speak of everything that happened to the watch before it left the factory as constituting its heredity, and everything that happened to it after that as its environment. A division might also be made at a point before the parts were assembled.

The analogy with human abnormalities is obvious. We usually accept the results of injuries and unfavourable agencies that affect the organism after fertilization as environmental, and all relevant previous circumstances as part of its hereditary nature. The time sequence of the previous events, however, is of great interest. Instead of attempting to ascribe our causes to either nature or to nurture, we can simplify the objective and merely ask which of two causal events was the earlier. In practice it is convenient to divide the developmental time-scale into various epochs, as is shown in Table XVII. Causes which act in the

TABLE XVII

TIMING OF POSSIBLE CAUSES OF MENTAL DEFECT

Usual Terminology	Epoch	Agency
A. Genetical, hereditary, endogenous, due to nature	(i) Remote	Spontaneous mutation in ancestral germ cells
	(ii) Recent	Spontaneous or induced mutation, meiotic errors in parental germ cells
B. Environmental, exogenous, due to nurture	(i) Early prenatal	Injury to the fertilized ovum during early stages of development, maternal disease
	(ii) Late prenatal	Intrauterine disease, malnutrition, infection, incompatibility
	(iii) Intranatal	Abnormal birth
	(iv) Postnatal	Diseases or accidents in infancy or childhood; unfavourable social environments

pre-conceptual period, before the formation of the individual zygote, are usually classed as hereditary

The temporal arrangement of causes is significant in relation to the problem of treatment. Palliative or curative measures can indeed be attempted with any disease irrespective of the time of the origin. Cataract, whether hereditary or acquired after injury can be treated by the ophthalmic surgeon and it is almost immaterial to the physician prescribing insulin whether diabetes is due to inborn metabolic infirmity or intercurrent disease. Preventive or radical measures, however, are directed so that the disease is attacked at its source. The more recent the occurrence of a disturbance, which is responsible for existing cases of defect, the more easily will it be controlled and eliminated as a cause of new cases in the future.

#### HEREDITARY MATERIAL

Animal bodies are built up of units called cells. Each cell is surrounded by a membrane or wall and contains many complex structures. Some of these, including the chromosomes, are contained in the nucleus, a compact object separated from the rest of the cell contents which are known as cytoplasm. The nucleus contains the hereditary material in the form of strands of desoxyribonucleic acid (DNA) and this is the main component of the chromosomes. It is believed to carry a kind of code determined by its minute structure—that is to say the ordering of its nucleotide bases. The code acts as an instruction for synthesizing chemical substances like proteins, which are needed for the functioning of the cell. In man, as in nearly all living things, DNA occurs in the form of a double spiral strand. In the process of replication the two strands separate and each builds a new partner (Szybalski and Djordjevic 1960).

It is believed that the DNA acts by virtue of an intermediary substance, known as ribonucleic acid (RNA) which conveys the information from the nucleus into the cytoplasm. The chromosomes themselves are not simple chains of DNA, they contain also RNA and protein (Kaufmann, 1957). However they seem to be composed of a series of items of instructions as there might be in a tape recording. Each separate instruction, which determines a specific molecule, such as an enzyme, can be called a gene. Instructions can be varied in the same region and there



can be more than one enzyme of almost the same kind produced in different people. It is not yet clearly established exactly how a gene should be defined but it is probably represented by quite a long strip of DNA tape.

Variants of the same instruction, leading to the formation of slightly different proteins, are called allelic genes, alleles or allelomorphs. The position of a gene on the chromosome is termed its locus so that, at one locus, there can be many alleles. Examples in man are the sets of genes which determine the ABO blood groups or the different haemoglobin chains in A, S and C.

In man the hereditary material is divided into 46 sections of varying lengths making 23 different sorts of chromosomes. Each type of chromosome is represented twice in ordinary somatic cells so that there are altogether 23 pairs, or 46 individual chromosomes. A pair of homologous chromosomes, as two of the same type are called, contain comparable sets of loci. At some points the genes on the two members of the homologous pair may agree. They are then said to be homozygous at the locus. Or they may contain different alleles. In such a circumstance they are said to be heterozygous.

These arrangements apply to 22 pairs of chromosomes, known as autosomes. For the remaining pair, the sex chromosomes, there is an exception in the male. He has two morphologically very different sex chromosomes, an X and a Y, (see Figure 4 and Plate VIIh) although the female has a homologous pair, XX.

Transmission of the hereditary material from one generation to the next takes place through germ cells or gametes. These cells, sperms in the male and ova in the female, have half the normal complement of chromosomes when they are fully mature. The process of maturation involves two cell divisions of a special character, called meiotic, in the first of which the number of chromosomes is halved. The new individual of the next generation, known as the zygote, is formed by fusion of a male and a female gamete. Thus each normal person has received one half of his chromosomes from each of his parents.

Meiosis in man has been studied intensively in the male but not yet in the female. All the ordinary preparations of human chromosomes are made from somatic cells in the state of

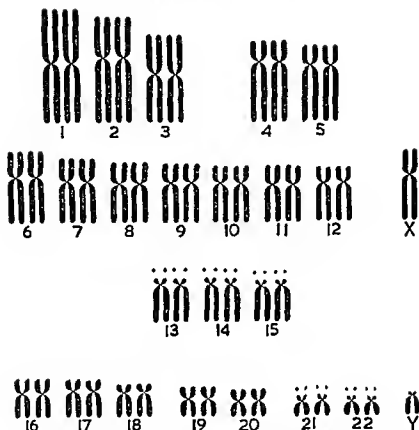


Figure 4 —Diagram of human (male) mitotic chromosomes

The autosomes are arranged in homologous pairs according to the Denver system. Nos. 1, 2, and 3 are sometimes classified as Group A, 4 and 5 as Group B, 6 to 12 as Group C, 13 to 15 as Group D, 16 to 18 as Group E, 19 and 20 as Group F, and 21 and 22 as Group G. The sex chromosomes are X and Y. A normal female would have two X chromosomes and no Y. Pairs 13, 14, 15, 21, and 22 carry small bodies, known as satellites, attached to the short arms.

**mitosis** At one point, during metaphase, each of the 23 pairs can be clearly seen, in suitable conditions, with the light microscope.

#### MUTATIONS

Genes have to be copied at every cell division. The process of copying occasionally goes wrong (Haldane, 1932a) and this is termed *gene mutation*. An allele which produces disharmony

io developmeot must have arisen by mutation at some definite point in time, such a time may have been remote or recent. Experimental geneticists have found that mutant genes, responsible for all kinds of abnormalities, are constantly arising afresh but the rate of mutation at any one locus is usually very slow as compared with the life history of the animal concerned. In the fly *Drosophila melanogaster* the upper limit of spontaneous mutation frequency for a single gene is about once in 10,000 life cycles. The usual rate is probably less than one in a million life cycles. Some genes are more liable to mutation than others. Reverse mutation back to the original form is also possible.

Muller (1927) showed that the mutation rate could be increased artificially by exposing flies to X-rays or to  $\beta$  rays from radium. Previously known spontaneous mutation rates were thus speeded up 150 times. Heat, according to Goldschmidt (1929), can have a similar effect and so also can ultra violet light. Auerbach and Robson (1947) found that mustard gas could cause an increase in mutation rate. Other poisons, like phenol and certain carcinogenic substances (Demerec, 1947), have been proved to have comparable properties. Moreover some gene loci are especially sensitive to one agent and some to another. Induced mutation is, for practical purposes, an environmental effect which changes the hereditary material. The subject is discussed in the M R C Reports (1956, 1961).

Another sort of mutation, which can be spontaneous or induced, is not a change in a single gene but a breakage or a rearrangement in one or more chromosomes. Rearrangements, which involve no alteration in the total amount of active hereditary material, are not harmful to the individual and may be transmitted through many generations. They are, however, liable to produce disturbances in meiosis. Consequently, gametes with excess or deficit of chromosomal material may be produced and lead to abnormal offspring. Soell and others (1934, 1935) induced rearrangements of chromosomes in mice by exposure to X-rays. They found that a proportion of the descendants of irradiated parents had unbalanced sets of chromosomes and were consequently malformed, often with gross defects of the neural tube. In man, the inheritance of such conditions may give rise to pedigrees where, for several

generations, malformation is transmitted by normal parents and recurs irregularly in collateral relatives

A third type of spontaneous or induced hereditary change, which is not usually called mutation, concerns alterations in the number of chromosomes occasioned by errors in the mechanics of cell division. The most usual type is called non disjunction and here two homologous chromosomes both go to one daughter cell, and none to the other, instead of one to each. The result is that new cells with one too many and one too few chromosomes are formed. When this occurs in meiosis, abnormal germ cells are formed and subsequently abnormal zygotes. This is the usual cause of mongolism. When non-disjunction occurs in mitosis the result may be to produce an abnormal line of somatic cells and the individual who possesses them is said to be mosaic. A disturbance of this kind, which occurs in the early stages of embryonic development, may cause severe malformation (see p. 184).

All kinds of mutations, although they apparently arise in most instances spontaneously or in response to environmental agencies, may also be influenced by genes. There are so called mutator genes which cause other genes to mutate faster than usual. Genes are also known which disturb meiosis and cause non disjunction in gametogenesis (Sturtevant, 1929). Abnormal offspring are produced by parents who carry such genes. Other factors, like the "sticky" gene in maize described by Beadle (1932) can affect both meiosis and mitosis and so may lead to mosaicism.

#### GERM PLASM INJURY

In the nineteenth century it was generally believed that spontaneous changes in the germ plasm were of rather frequent occurrence. Darwin accepted this view because he saw that spontaneous hereditary variation was a necessity in the mechanism of evolution. The causes of mutation were unknown, popular, as well as medical, doctrine held that external poisons could injure the germ cells. In spite of the teachings of Weismann (1893), who propounded the principle of the unchangeable nature of the germ plasm, medical authorities clung to the older viewpoint. It was not unusual for alcohol, lead poisoning or toxins produced in organic diseases, such as

syphilis and tuberculosis, to be credited with the power of altering the parental germ plasm in such a manner as to produce monstrosities in the offspring. Plumbism in the father has been considered responsible for stillbirths by Paul (1860) and responsible for epileptic defect by Thomson (1923). Savage and Goodall (1907) believed that phthisis in a parent increased the tendency to nervous disorder in the offspring, and Langdon Down (1866) believed that it could cause mongolism. The effect of poisons on the germ substances was termed, by Forel (1911), "blastophthoria", from the Greek *βλαστός*, a bud or germ, and *φθορά*, destruction. It was asserted to be a very important element in the causation of mental diseases and defects by Myerson (1923). Tredgold (1937) subscribed to the doctrine that many different environmental factors could effect changes in the germ cells and thus cause mental defect.

In view of the recent discoveries on chemical mutagens the subject cannot be lightly dismissed. However, we must ascertain that the concentration of a noxious substance in contact with the germ cells is high enough to have a reasonable probability of being effective. In the case of alcoholism, for example, this likelihood seems remote. Experimental work on animals has sometimes appeared to support the theory of alcoholic blastophthoria, in particular the work of Stockard (1923). The parental generations of guinea-pigs were subjected to alcohol fumes and it was claimed that the offspring were frequently malformed in consequence of germ plasm impairment. Subsequent workers, Durham and Woods (1932), were not able to obtain the same results. Bourneville and Leflaive (1884) attributed human hydrocephaly, and numerous malformations leading to idiocy, to spirit-drinking by the parents. Moreover, Bertholet (1909) maintained that alcoholism in a male could cause histologically demonstrable pathological changes in the testes. Later researchers have not tended to substantiate such claims. It was demonstrated by Elderton and Pearson (1910) that the children of alcoholic parents were not inferior but, if anything, superior physically and mentally to those of abstinent parents, though these opinions were disputed (Keynes, 1910). In the Colchester Survey, the children of alcoholic parents were found no less numerous and no more often defective than the children of non-alcoholic parents of

*similar mental grades* It used to be thought that alcoholic intoxication of parents at the time of intercourse could affect the offspring adversely, but it is difficult to understand how a concentration of alcohol sufficient to injure the spermatozoa or ovum could be achieved The possibility that spermaticidal chemical substances, such as lysol, deliberately used in douches with a view to contraception, might harm some spermatozoa and cause mutation in them, but fail to kill them, has to be considered At present there does not seem to be any tangible proof of the existence of this factor as a cause of congenital defect

The effects of irradiation on the germ cells, and the production of abnormalities in the offspring by new mutations thus induced, have recently been studied from several points of view Haldane (1947) calculated the total number of deaths from recessive mutations which might result from an atomic explosion These would be spread over very many generations and it appears that they would form only a small fraction of the number of immediate deaths The load of mutations (Muller, 1950) is in danger of being increased by the common use of X-rays in medicine, by occupational hazards in specific industries (Haddow, 1952) and from the fall out produced by nuclear test explosions Nevertheless, direct measurement of the genetical effects of radiation in man is extremely difficult mainly because the expected changes in any given generation would be very slight Examination of the offspring of irradiated parents (Neel and Schull, 1956, Crow, 1955) has provided essentially negative results The only positive findings are the indirect observations on sex ratio (Turpin, Lejeune and Rethore, 1956, Tanaka and Ohkura, 1961) which suggest that some daughters of exposed fathers and the sons of exposed mothers failed to develop because of damage to genes on the parental X-chromosomes

#### ANTICIPATION

It has been claimed that when germ plasma is vitiated there is often a tendency for it to continue to degenerate for a long period If so, the second generation of animals is more severely affected, more grossly malformed than the first generation of abnormal offspring The process is said to lead to "anticipation" in the sense that the onset of the disease in affected individuals

is earlier in every succeeding generation Mott (1910) strongly upheld this hypothesis, maintaining that, by virtue of anticipation in hereditary diseases, "rotten twigs were continually broken off the tree of life" The additional assumption of the existence of protean influence, known as the "neuropathic diathesis", which was a contributory cause of all mental and nervous diseases, was proposed by Tredgold (1929) to account for the presence, in the same pedigree, of various types of insanity and defect Once injured, the germ plasm was capable of a wide range of manifestation beginning with mental illness of comparatively late onset, or psychopathic temperament, in one generation and culminating in idiocy in the remote offspring

The main difficulty in accepting the hypothesis of anticipation is its lack of support from experimental observations The effects of mutation remain the same, but their manifestations may vary considerably according to the rest of the genetical constitution of the individual and in response to the environment In the study of human families, the apparent occurrence of anticipation is very frequently observed especially with respect to conditions whose range of onset age is wide, as in mental illness (Rudin, 1916) The phenomenon is not confined to deleterious qualities Galton (1869) stated that "the sons of gifted men are decidedly more precocious than their parents I do not care to quote cases, because it is a normal fact analogous to what is observed in diseases and in growths of all kinds, as has been clearly laid down by Mr Darwin" However, there are good reasons for supposing that the cause of the phenomenon lies in the special selection of data, which is inevitable in collecting human material, rather than any natural peculiarity of the germ plasm itself

The span of life and the generation time in man are very lengthy as compared with the period during which any family is kept under close observation Very commonly, familial instances of disease are only discovered because a parent and a child are both found to become affected at about the same time When this is so, the parent, who will be on the average some 25 to 30 years older than the child must have developed the disease 25 to 30 years later in life than the child For example, if a father and son both appear on the books of a mental

hospital within the space of a few years, the onset of acute mental illness will be found, almost invariably to be at a later age in the father than in the son. The parent suffers from, say, an involutional condition with onset at the age of 55 and the son from a psychotic episode at about the age of 30. If three generations are represented simultaneously in a mental hospital, the effect is accentuated and we may find a grandparent suffering from senile insanity coincident with a very early psychosis or mental defect in the grandchild. The complementary families in which disease has an early onset in the parent, say at 30 years, and the equivalent condition does not develop until the age of 55 in a child, born when the parent is 25, will rarely be observed. A period of 50 years must elapse between the onset of the disease in the parent and the onset in the child. Unless families are observed for very long periods, such cases will undoubtedly be missed. The exclusion of instances that show the converse of anticipation is assisted by the comparative infertility of individuals, who suffer from chronic mental or physical diseases beginning early in life and who consequently tend to be infertile. Cases in which the parent had idiocy and the child senile psychosis never occur because of the infertility of idiots and not because an underlying hereditary influence undergoes a progressive change for the worse.

#### GENE MUTATION AND SELECTION

Whenever a gene has among its possible manifestations the effect of making its possessor totally infertile, one particular specimen of the gene will be lost to the race. In ordinarily stable conditions, that is, when a population is genetically constant, this loss is balanced by fresh mutation. If this were not so, all the genes producing hereditary defects associated with infertility would have been eliminated in past ages by natural selection. In the absence of new mutation, dominant defects are rapidly eliminated from the population but, for recessive defects, the process is exceedingly slow. There are, however, exceptions because a gene which, in one setting reduces fertility can in another setting cause increased fertility and these two effects might equalize. The conditions of equilibrium and the rate of natural selection under different conditions have



been intensively investigated by Fisber (1930), Haldane (1932a) and Wright (1931)

The mutation rates, of human genes which cause lethal defects, can be estimated on the assumption that the population is in equilibrium and that gene loss through infertility is made good by mutation. Such estimates are provisional because of possible counterbalancing influences, the most important influence concerns hybrid vigour, or heterosis, as discussed in Chapter VI. The typical pedigree where new mutation can be confidently postulated is one in which a condition known to be regularly dominant appears sporadically, that is, without affected parents.

#### DOMINANT CHARACTERS

In human genetics, it is customary to speak of genes, which produce marked effects in single, or heterozygous form, as dominant. It is, however, the inherited character or disease which is dominant, not the gene. It would be accurate to refer only to heterozygous genes.

Rare dominant traits in man have characteristic pedigrees. In the standard case, where the presence of the gene is manifested in every heterozygote, three criteria are to be satisfied:

- (i) There is sharp distinction between affected and unaffected persons in the same family.
- (ii) Every affected person has an affected parent.
- (iii) Approximately one half of the children will be affected in every sibship when there is an affected parent.

Few inherited diseases agree precisely with these specifications. In most of them, as emphasized by Grüneberg (1947), the number of steps between the gene and the clinical result is large. Consequently, the final manifestation of the gene may be modified by actions of the other genes present in the individual, by environmental causes or even by quite unpredictable circumstances, which some investigators prefer to call the effects of chance. The result in pedigrees is to produce irregular modes of transmission, which are highly characteristic of dominant diseases associated with mental defect or mental illness.

The time honoured method of presenting pedigrees with black spots to signify affected cases is misleading and conceals the complexity of the material. Even in such a typically

dominant condition as Huntington's chorea, there is much variation in manifestation of symptoms and in the age of onset. As a rule in hereditary diseases, age of onset is closely allied to severity, for if the age of onset is very late, this is biologically equivalent to a mild case with average time of onset. Skeletal deformities, which show very strong dominance in some families, like ectrodactyly (absence of digits), in other families are quite irregular. The path of transmission of the heterozygous gene may be evident from the pedigree (Hanhart, 1945), in spite of many skipped generations. Accordingly, if a condition known to represent a single heterozygous gene arises in a pedigree without any known ancestor's having had the defect, it is not always safe to assume that there has been a recent mutation, though this is often an attractive hypothesis.

The student of human pedigrees should also be warned that sometimes conditions that appear clinically identical or only very slightly different may represent entirely different genes leading to approximately the same end results by diverse processes, as in some of the different forms of hereditary ataxia or the myopathies. When two or more distinct conditions are very similar clinically and differ only in age of onset, the hypothesis that they are due to two or more allelic genes may be entertained. A further complication may arise on account of the interaction of allelic genes. Sometimes one or other of the series of possible allelic partners may alter the dominance of the main pathological gene and produce characteristic irregularities of inheritance. This may be the case in dystrophia myotonica (Goldschmidt, 1938), where there is little relationship between the severity of the disease in the parent and that in the children but close similarity in sibs.

A dominant condition due to a single gene may be differently manifested in the two sexes (sex influence) or confined to one sex (sex limitation). An example is early baldness, which is almost confined to men (Harris, 1946). Care is needed to distinguish sex limited genes from genuinely sex linked genes in pedigrees.

#### RARE RECESSIVE CHARACTERS

Completely recessive characters do not manifest themselves in heterozygotes and only produce effects in homozygotes who

possess the same pathological gene in duplicate. These two similar genes must have been inherited, one from each parent. The rules for the recognition of a rare recessive condition follow from these facts. They apply to diseases with an incidence not greater than about one in 1000. Detection of common recessive traits is less straightforward.

(i) Affected and unaffected persons in the same family can be sharply distinguished.

(ii) Parents and all immediate ancestors are unaffected.

(iii) Father and mother are found to be blood relatives more frequently than expected from the consideration of the general population rate of consanguineous unions.

(iv) More than one offspring is likely to be affected. The proportion of affected in a series of small families will usually exceed the Mendelian expectation of one quarter but it will approach one-quarter in large sibships. This is a statistical consequence of the mode of selection of sibships by the presence of at least one affected member.

(v) Occasionally cases occur in collateral branches of the same family group.

Since recessively determined diseases can, and usually do, arise in families where parents are perfectly normal, the effect of natural selection upon the genes responsible for them is very weak. Types of mental defect known to be due to recessive genes, like amaurotic idiocy and phenylketonuria, appear quite unexpectedly in families, and undoubtedly have been doing so for thousands of years in spite of the fact that the sufferers are themselves almost always infertile. The genes are carried on in the general population unobtrusively and their presence only comes to light when two carrier parents have an affected child, an event which occurs only in one fourth of their children.

Although two abnormal mutant genes are eliminated each time an infertile recessive type is produced, it is not wise to infer that this loss has to be made good by new mutation in a stable population. The incidence of a rare recessive disease fluctuates rapidly if the degree of inbreeding alters. Moreover, if the carriers of the gene should be even very slightly more fertile than the rest of the population, this could counterbalance the rare loss of genes in the infertile homozygotes.

The visible effects of genes are subject to modification both

by environment and extraneous individual constitution. The range of variation of recessive diseases, however, is found to be more restricted than that of dominant diseases. Fisher (1930) pointed out that perfectly regular dominance of an abnormal gene is a very unusual phenomenon. He supposed that modification of the effects of harmful dominant mutants gradually progressed in a favourable direction under the influence of natural selection. He attributed the partial suppression of the harmful genes to the accumulation of hereditary traits which make the disease milder. A dominant mutant tends, thus, to acquire more and more the properties of a recessive trait. Natural selection cannot easily proceed further than this. Its action upon homozygotes is very slow. Hence, progressive favourable modification of abnormal recessive traits by the same method is not to be expected. Theoretical objections have been raised against Fisher's theory by Haldane (1930), but it is a stimulating idea and may help considerably in the interpretation of the genetics of human defects.

#### INCOMPLETELY RECESSIVE CHARACTERS

Some genes have effects which have been termed intermediate between dominant and recessive. The colour of the Andalusian fowl is normally black, but a dominant mutant gene makes it bluish grey (Bateson, 1913). When two such genes are present, the bird is white with only small splashes of dark pigment. Thus the dominant, i.e. the heterozygous, type is intermediate between the normal type and the recessive or homozygous type. In man also, this type of inheritance occurs. It has been described, for example, in Cooley's anaemia or thalassaemia major (Valentine and Neel, 1944). Here, in the heterozygous form, the gene produces an ordinary dominant character, thalassaemia minor, a mild chronic anaemia. If two heterozygotes mate, one-quarter of the offspring are severely anaemic homozygotes. If the heterozygous condition should be exactly intermediate between those of the two corresponding homozygotes, it is more convenient to classify the genes concerned as perfectly additive.

Certain types of mental defect may be due to genes with additive tendency, and some pedigrees can be so interpreted. The family shown in Figure 5 contained defectives of all grades,

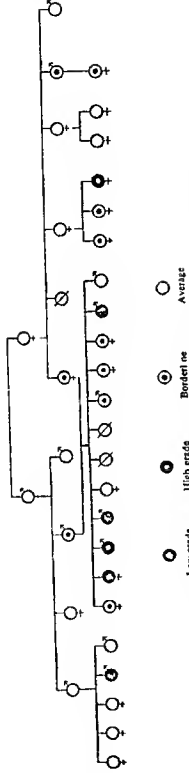


Figure 5 —Pedigree showing mental defect of no specific clinical type.

The low grade cases here are apparently due to an incompletely recessive gene i.e. one with approximately additive effects

but none was of any known specific type. Since the parents of the large sibship with three cases of severe defect were cousins, the hypothesis of recessive inheritance for these cases of imbecility and idiocy can be reasonably entertained. However, both parents and several other members of the family showed signs of mental inferiority, not amounting to severe defect but varying from mild defect to apparently normal mentality. This relatively mild subnormality shows an irregularly dominant type of inheritance which could be attributed to the same gene that caused the severe defect in homozygotes.

Human genes which cause rare recessive diseases do not usually give rise to obvious effects in the heterozygous carriers. In an increasing number of instances, however, carriers have been found, by the application of specific tests, to be slightly abnormal. Examples relevant to the study of mental defect are phenylketonuria and galactosaemia. Genes responsible for characters which cause common variations are more often clearly additive in their effects. In fact, from the genetical analysis of normal variations in stature or intelligence, it has usually been inferred that these are due to the combined additive effects of a large number of genes at different loci.

### SEX-LINKED GENES

In man, sex-linked inheritance or transmission of genes on the X chromosomes presents very noticeable peculiarities in pedigrees. The rules for the recognition of rare sex linked recessive traits can be summed up as follows:

(i) Males are almost exclusively affected and they are distinct from normal males.

(ii) Approximately one half the males in an affected sibship show the condition and half the females are carriers. Female carriers are unaffected when the gene is completely recessive.

(iii) Both parents are normal nearly always but maternal uncles are often affected. The sons of the sisters of an affected male, or of his maternal aunts, can be similarly affected. An affected father cannot transmit to his son.

(iv) In the extremely rare case of an affected female, her father and all her sons must also show the condition.

(v) There is no history of any male or female affected relative in an appreciable proportion of instances. In some of

these families the disease may have arisen by fresh mutation.

A few rare diseases associated with mental defect are transmitted in this manner, notably certain types of hydrocephaly, microphthalmia, myopathy and oculorenal osseous dystrophy. In general, the genes on the X chromosome do not play any greater part in the causation of mental defect than might be supposed from the fact that there are 22 autosomes to one sex chromosome in man.

It is not easy to detect phenomena which could be ascribed to sex-linked genes even in quite large quantities of pooled data. If the relevant alleles are common, or incompletely recessive, in the female, fathers tend to resemble their daughters and not their sons, and mothers resemble their sons more than

TABLE XVIII

A TEST FOR SEX-LINKED GENES AS CAUSES OF MENTAL INFERIORITY

Comparative Mental Grades of Parents and Sexes of Offspring	Grades of Offspring (patients and their sibs)						Total
	Superior	Average	Border-line	Feeble-minded	Imbecile	Idiot	
(i) Father superior to mother Sons	4	252	100	114	55	24	549
(ii) Father inferior to mother Daughters	0	136	50	33	21	5	245
Total	4	388	150	147	76	29	794
Percent in each grade	0.5	48.9	18.9	18.5	9.6	3.6	100.0
(iii) Father superior to mother Daughters	4	211	109	130	47	17	518
(iv) Father inferior to mother Sons	1	127	47	44	14	8	241
Total	5	338	156	174	61	25	759
Percent in each grade	0.7	44.5	20.6	22.9	8.0	3.3	100.0

If common sex-linked genes are significant factors in determining mental grade, the offspring in classes (i) and (ii) should be inferior to those in classes (iii) and (iv). This is, however, not so except possibly in the severe grades.

their daughters. Hence, if defective fathers had more defective daughters than sons, and *vice versa*, genes on the X chromosome could be blamed. The Colchester Survey brought to light 240 patients whose fathers were judged to be of higher mental grade than their mothers and 93 patients whose fathers were definitely of lower mental grade than their mothers. In Table XVIII the male children in the families where the mother was inferior and the female children in the families where the father was inferior are grouped together. If sex-linked factors were significant causes of variation in mental grade, these classes should contain more defectives than the two remaining possible groups of offspring. In this sample no appreciable difference in mental grade between the two groups of offspring is noticeable. The conclusion may be drawn that there is no outstanding tendency for sex linked genes to influence the genetics of mental deficiency.

Another type of sex-linked inheritance, called partial sex linkage, could occur if the responsible gene is located on that portion of the sex chromosomes where crossing-over may be supposed to take place between the X and Y chromosomes (Haldane, 1936). The criterion for supposing a gene responsible for a defect to be so located is that it is transmitted from a father to his sons, if he has received it from his father, and that it is transmitted from a father to his daughters, if he has received it from his mother. A possible example is total colour blindness (Tanaka, 1957). There is no evidence that such genes play any part in the causation of mental defect.

Another peculiar kind of inheritance would be shown if a trait were caused by a gene located on the part of the Y chromosome which does not cross over with the X chromosome. This would be transmitted from fathers to all their sons and would never appear in any female. The character of maleness itself is the only trait of this sort so far proved to exist in man.

#### INHERITANCE OF CHROMOSOME ABERRATIONS

The possibility that some human malformations and defects might be associated with chromosome aberrations has been in the minds of many observers for a long period. Especially notable are Waardenburg's (1932) suggestion that non-disjunction might account for mongolism and Haldane's (1932c) early suppositions that the sex chromosomes were



abnormal in intersexes and the autosomes unbalanced in some malformations

Since most of these conditions are sporadic in occurrence and not familial it must be generally supposed that the aberration had occurred first not further back than in the parental gonadal tissues. Most cases of sex chromosome aberrations with gonadal agenesis seem to arise in this way, for example the XXY Klinefelter males and the single X Turner females. However, the special inheritance of defects originating from abnormal gametogenesis in normal parents with balanced translocations should have characteristic features. The balanced translocation can be transmitted for several generations without producing any noticeable effects. Then, in one or more collateral sibships, the same or related type of malformation appears. Sometimes, perhaps in successive generations, in one line of descent through normals, sibs are affected. Similar results could follow from the presence of inversions, harmless in themselves, but leading occasionally, in germ cell maturation, to the production of abnormal gametes. The error results from difficulties encountered in the pairing of poorly matched homologous chromosomes.

Certain pedigrees of mongolism, like that of Fantham (1925), suggested that peculiar chromosomal mechanisms might be operating (Penrose, 1939f) and recently balanced translocations have been proved, by cytological examinations, to be present in parents and grandparents of mongols in some critical families. Other translocations, involving quite different chromosomes, have been observed to predispose normal individuals to have malformed offspring (Edwards, 1961) and no doubt many other examples will be discovered.

When the individual with an unbalanced chromosome complement has offspring, it is inevitable that some of them will be unbalanced like their parent. The effect of this in a pedigree is the same as that produced by a rare dominant trait. Most mongols, for example, arise from primary non-disjunction, as described by Lejeune, Gautier and Turpin (1959), occurring in the ovum of a normal mother during oogenesis. In the rare event of a mongol's having offspring, the child may be a mongol by inevitable or secondary non-disjunction during maturation of the ovum in the affected mother, as shown by

Hanhart, Delhanty and Penrose (1960), and by Stiles and Goodman (1961)

#### MATERNAL GENETICAL INFLUENCES

Besides the genes situated on the chromosomes in the cell nucleus, the cytoplasm of the cell may contain transmissible particles, called "plasmons" by von Wettstein (1928). Such phenomena have been extensively studied in protozoa by Sonneborn (1949) but very few instances have been established in multicellular organisms. Since the sperm cell contains very little cytoplasm, plasmic substances must be inherited almost entirely by way of the ovum. It is a possibility not to be overlooked in human pedigrees, if a disease affecting both sexes equally is always transmitted through the mother. Leber's hereditary optic atrophy, which sometimes appears in association with mental defect, might be inherited in this way (Imai and Moriwaki, 1936) but this is very doubtful.

The action of some genes is delayed, in that they affect the next generation and not the individual who carries them. For instance, the liability to twinning in cattle has been attributed to a recessively determined trait in the mother. Similarly, Bonnevie and Sverdrup (1926) have suggested that a recessive factor in the human mother makes her liable to give birth to twins. Hammond and Walton (1934) found that in rabbits a particular maternal constitution, inherited recessively, was responsible for producing a high proportion of atrophic foetuses. The gene which, in homozygous form tended to induce chromosomal non-disjunction, described by Sturtevant (1929), only affected the ova. To investigate the possibilities of such transmission in man, the occurrence of abnormalities in the children of sisters would be sought. When dealing with a rare condition, the pedigrees would also be examined for consanguinity in the mother's parents.

Another method of gene action arises when there is a specific genetical difference between mother and foetus. Such disparity is significant with respect to the *Rhesus* series of genes. Typically, the mother lacks an antigen, because she is homozygous for a gene which fails to produce this antigen, but the foetus inherits the antigenic gene from its father. The familial picture will be to some extent, similar to that found when a maternal recessive

factor is directly responsible for disease in the offspring. However, when there is antigenic incompatibility the paternal side of the family may show affected individuals. The father himself might be affected though the mother could not be.

#### MATERNAL ENVIRONMENTAL INFLUENCES

The environmental influences, which act adversely upon the growing embryo from the time of fertilization of the ovum until birth, are very numerous. Physical agents, nutrition, chemical agents and infections are all of importance at this stage. Details are given in Chapter X. In addition, there are effects connected with maternal age and parity.

Although the means by which the foetus is influenced is obscure, there is little doubt that the age of the mother is very significant in the aetiology of malformations. In mongolism the effects of maternal age are particularly noticeable, since half the known cases are born at the maternal age of 36 years or later. In many other malformations, some caused by chromosomal aberrations and others, like congenital hydrocephaly, probably not, a similar but less striking relationship has been observed. The incidence of twinning, mainly dizygotic, also increases with maternal age. The prevalence of multiple births in the later maternal age groups (Duncan, 1866, Dahlberg, 1926) can perhaps be regarded as a slight biological compensation for the higher infant mortality in this range due to all types of foetal abnormality.

A disease dependent upon maternal age is difficult to separate aetiologicaly from one dependent upon the number of previous pregnancies (parity), because the two effects are so closely correlated. There is evidence that order of birth can have independent effect and that the first born, as well as those children born at the end of a long series of pregnancies, are less viable than those born in between, irrespective of the maternal age. Foetal malformations appear to be slightly commoner in the children of mothers having their first pregnancies (primiparae) than for the second and third. Ideas as to the possible reasons for these peculiarities are as yet in the speculative stage. Opinions are divided in implicating mechanical causes conditioned by uterine size, the maternal vascular condition and hormonal influences.

As already mentioned, if genetically determined differences in constitution exist between mother and foetus, the mother may become sensitized and form antibodies inimical to foetal development. Sensitization does not actually occur in every instance where it could occur and is very unlikely in first pregnancies. These maternal influences, though ultimately due to genes, are, from the point of view of the foetus, part of the intrauterine environment.

#### INTRANATAL ENVIRONMENT

The importance of abnormal birth conditions in the causation of lesions of the central nervous system and the implied significance in causing mental defect was emphasized by Little (1861). Since that time some investigators, notably Doll, Pbepls and Melcher (1932), have attributed practically all cases of cerebral diplegia to birth injuries. In a few cases, mental defect is certainly caused by injury at birth (Penrose, 1949). Most clinicians, however, recognize that the contribution of these accidents to mental deficiency as a whole is relatively small and that diplegias usually have other origins. According to Ebrenfest (1931), a large proportion of children are very slightly injured, when birth is quite normal, and new born infants often show signs of cerebral injury such as nystagmus. Prematurity is held to be a factor predisposing to cerebral injury because of fragility of the foetal blood vessels. Rydberg (1932) made an extensive study of the problem and concluded that serious signs of cerebral injury in the newly born infant are twitchings, spasms, rigidity, disturbances in breathing, cyanosis and drowsiness. Many infants who show these signs do not survive. Among the recoveries, some show marked mental retardation accompanied by persistent neurological signs. The importance of oxygen lack during birth and also prenatally has been stressed by Ingalls (1950).

#### POSTNATAL ENVIRONMENT

Any accident, which leads to a deterioration in the intelligence of a particular subject sufficient to imply social failure, may be considered a cause of mental defect. Postnatal injuries are undoubtedly important in certain cases but they are probably less often significant than infections. According to Winter and

Mainzer (1960), prematurity increases these risks. In order to evaluate the mental effects of accidents or diseases which cause cerebral injury, the history of ability before the event should be ascertained. Hereditary disease which becomes manifest at a special point in the life of the individual must also be excluded. Most of such hereditary conditions, however, are progressive, like cerebromacular degeneration or ataxia, whereas the effects of cerebral injury are usually stationary. *Difficulty arises when the predominant symptoms are those of behaviour disorder.* A behaviour disorder, developing in a person of fundamentally low intelligence, may give rise to a need for care and control as, for example, in a case of encephalitis lethargica. The disentangling of cause and effect, leading to the diagnosis of mental deficiency, can be very complex in such instances (Penrose, 1932). Another difficult type of case to diagnose can arise after cranial injury in childhood, in which behaviour disorder is marked although neurological signs are minimal and loss of intellectual powers only slight.

Finally, the training of a child and its emotional environment have to be considered. It is still a matter for investigation to determine how far a psychopathic, antisocial personality can be brought into being by unfavourable surroundings during infancy and childhood. Many authorities believe that this is possible and of frequent occurrence. Similar theories apply to the origins of some psychoses; mental illnesses, which develop early, may prevent a normal intellectual level from being attained (Bowlby, 1958).

#### METHODS OF DISTINGUISHING BETWEEN NATURE AND NURTURE

The problem of allocating the cause or causes of mental defects either to inborn or acquired characteristics with scientific accuracy has been shown to be much more complex than formerly supposed. When Galton (1875) first drew attention to the study of twins from this point of view, little was known about hereditary mechanisms. The principle, however, remains a good one. When each member of a pair of monozygotic twins has exactly the same genetical equipment, it can be supposed that any dissimilarity between them which is manifest must be due to different environmental agencies. This

statement requires qualification, for some developmental processes are asymmetrical. Just as the two sides of the body are unlike though they carry the same genes, so one monozygotic twin can differ naturally from the other in spite of having the same constitution. Furthermore, the environments for monozygotic twins, even for those separated at birth and subsequently reared apart, are similar during gestation. The maternal age, parity and state of health are the same for both, so that to some extent such twins are congenitally similar as well as genetically similar. In so far as this is so, the study of twins differentiates between happenings before and after birth rather than between happenings before and after conception. It is a remarkable fact that conjoined twins tend to be much less similar to one another than monozygotic twins who develop separately. In extreme cases one of the pair can develop normally, or almost so, while the other may remain a collection of rudimentary parts. Whether these marked differences found in conjoined pairs can properly be attributed to peculiarities of environment is doubtful. Dahlberg (1945) has made the suggestion that, when there are no genetical or environmental causes evident, we are justified in ascribing twin differences to chance. One such circumstance can arise if a mitotic error or a mutation occurs in one twin but not in the partner.

The comparison of identical twins with fraternal, on the assumption that, for dizygotic pairs, the environment is just as constant as for the monozygotic, is also misleading. Fraternal pairs are genetically just as much alike as ordinary sibs, that is brothers and sisters. Maternal factors are constant for both types but postnatal environment is usually more dissimilar for dizygotic than for monozygotic pairs. Hence the importance is evident of not drawing inferences about the maximal effect of environment from the study of monozygotic twins.

One other point needs attention, namely the method of deciding whether or not a pair of twins is identical. The probability of genetical identity is increased by every similar trait found in the two (Maynard Smith and Penrose 1955). Some traits are more valuable indices than others. Sex normally, must agree in monozygotic pairs and serology is extremely useful as a method of excluding cases who differ in any antigen. Physical measurements are convenient, but not always conclusive. Eye colour is

a good character bere because it has so many genetical determinants, but it fails in rare instances of heterochromia. Evidence from dermatoglyphs, including finger ridge counts, has proved a valuable instrument for the practical diagnosis of zygotic type.

Another method of attempting to assess the significance of postnatal factors on the development of the individual's intelligence and behaviour is to compare adopted children taken to new homes with their sibs who remain in the original home surroundings. Unfortunately, for purposes of research, many adopted children are those whose parents are unknown, often they have no full sibs.

Yet another method of comparing nature and nurture is based upon the assumption that environmental factors, which cause variations in any character we desire to study, are evenly distributed over the whole population. The expected degree of likeness between relatives, on the assumption that all variations are genetically determined, is then calculated and this degree is compared with the observed likeness. If the observed value agrees with the expected value the only significant source of variation can be held to be heredity. For example, on the basis of certain assumptions about the mode of inheritance of stature, the expected likeness between sibs would be equivalent to a correlation of  $+0.5$ . Since the likeness of stature in sibs has been found to be of the same order by several different observers, it can be argued that environment plays little part in determining stature. The argument, however, cannot be quite sound, since stature is undoubtedly affected by nutrition.

The basic assumption that environment is evenly distributed is of doubtful validity. Environment can be similar for members of the same family group, and so a family likeness is produced in non hereditary characters. The effect is strengthened when families in different social and occupational groups are exposed to quite different extremes of environment. Another point, emphasized by Hogben (1933a), is that even if a cause is too infrequent to disturb materially the average likeness measured between relatives, it can still be socially important. The types of environmental agencies which can alter intelligence for better or for worse are elusive but are probably just as real as those, like malnutrition, which can affect physical size.

## INTELLIGENCE OF TWIN PAIRS

The intellectual similarities of monozygotic twin pairs were noted by Galton, but the first psychometrical study in this field was made by Thorndike (1905). The resemblance of twins in mental traits was found to be twice as great as that for ordinary sibs. Merriman (1924) made a much more extensive study, testing 200 twin pairs with the Stanford-Binet, and he separated the two types, monozygotic and dizygotic, from one another. He showed that twinning itself was not associated with any mental handicap, and he also concluded that environment was insignificant as a cause of twin resemblance. Tallman (1929) used the same method, which consisted of finding the mean difference in score for pairs of children. Since the difference can be positive or negative, a better index would have been the mean square difference, which is equal to twice the "variance" or square of the standard deviation within the group of pairs used. However, 63 identical twin pairs differed, on the average, by 5.1 points, whereas 39 fraternal pairs differed by 7.4 points. From the assumption that the standard deviation of Binet I.Q. in the general population is 15 points, we can infer that the average difference to be expected between two children of the same age, tested at random, would be about 17 points.\* Tallman's group of non-twin sibs had an average difference in I.Q. of 12 points. Thus, not only were sib pairs more like one another than pairs of children chosen at random, but identical twins were, again, more alike than ordinary sibs. Twins of like sex and sibs of like sex were more similar than comparable pairs of unlike sex.

The ratio of the variance of twin pairs, or sib pairs, to the variance of all pairs in the same sample taken at random can be used as an index of their likeness in terms of correlation. Thus, if  $V_p$  is the variance of the twin pairs, i.e. half the mean of the squares of the differences between their measurements, and  $V$  is the total variance of the whole set of measurements calculated in the ordinary way, irrespective of pairing, then  $V_p/V = 1 - r_p$  or  $r_p = (V - V_p)/V$ . This value,  $r_p$ , is equivalent to

$$* \text{ Mean difference of pairs} = \sqrt{2/\pi} \times \sqrt{2} \times (\text{S.D.}) = \frac{2 \times 15}{\sqrt{\pi}} = 16.9$$

because mean deviation equals  $\sqrt{2/\pi} \times (\text{S.D.})$



the intraclass correlation coefficient of Fisher (1938). It is convenient to use this coefficient to express the likeness of twin or sib pairs. If monozygotic twin pairs were exactly alike in their intelligence measurements, their mean difference would be zero, their variance within the group of pairs zero, and their intraclass correlation unity. In reality, differences between monozygotic pairs exist and it is usually conceded that they represent, in the main, the effects of environment, though they may also be caused by inaccuracies of measurement. Presumably at least as much of the variance of dizygotic pairs is due to these same causes. On the other hand, similarities of environment, occasioned by the fact of their being twins, will tend to make dizygotic measurements more alike than corresponding measurements for ordinary sib pairs. Holzinger (1929) has suggested allowing for this by making the discrepancy between the variances of monozygotic and dizygotic twins (in terms of dizygotic variance) the decisive measurement of hereditary influence. That is, if  $V_m$  is the variance between monozygotic twins and  $V_d$  that between dizygotic twins, Holzinger's index,  $h^2$ , which is intended to measure the proportion of variation due to heredity in the trait concerned, is obtained thus:

$$h^2 = \frac{V_d - V_m}{V_d} = \frac{r_m - r_d}{1 - r_d}.$$

If the index has the value of unity, all variations in the trait are due to heredity; if it has the value zero, they are all due to environment.

The results reached by use of this formula must not be too rigidly interpreted, but are of intrinsic interest. Wingfield (1928) found, for example,  $r_m = 0.90$  for I.Q. in 42 monozygotic pairs and  $r_d = 0.70$  in 57 dizygotic pairs. The Holzinger index,  $h^2$ , is therefore 0.67 and can be interpreted as meaning that nature is twice as powerful as nurture. Newman (1942) gave values of the same index, 0.68 for Binet I.Q. and 0.80 for Otis I.Q.; for ability in science, the index was only 0.34 and for arithmetic tests only 0.12. For physical characters, like stature and weight, the indices were higher, 0.81 and 0.78 respectively. Herrmann and Hogben (1933) considered that hereditary influences accounted for about half the total variation in the intelligence measurements of children. Judged by twin data alone, heredi-

tary influence would be somewhat stronger. Thus,  $r_m$ , for intelligence measured by the Otis test, was 0.84 and  $r_d$  0.48, hence the Holzinger index would be 0.69. Holzinger (Newman et al. 1937) himself, using the Binet I Q, found  $r_m=0.88$ ,  $r_d=0.63$  and  $h^2=0.68$ .

Data of more immediate interest in relation to mental defect have been published by various investigators, who collected sets of twins one or both of whom were defective mentally. Rosanoff (1931) found 33 monozygotic both affected and 2 cases with one normal and one affected. Among the dizygotic twins, he found 32 both affected and 28 cases with one of the pair normal. Similar results were obtained by Smith (1929), who found the discrepancy between the two types of twins, with respect to mental defect, even greater. Surveys of this kind, however, must be interpreted cautiously. In the case of mongolism, for instance, by methods of twin analysis, it would appear that environment plays no appreciable part in the causation. This conclusion, however, is certainly false since unknown factors related to maternal age are undoubtedly very important in the aetiology (p. 207).

The fact that identical twins usually have very similar early environment makes it difficult for any method of twin analysis to give information about prenatal phenomena. Occasionally, however, cases of identical twins are noticed who differ very much in mental capacity at birth. In the pair described by Hobbs (1941), one child had a Binet I Q of 109 and the identical twin sister had a Binet I Q of 57, the discrepancy could have been due to injury of one twin at birth. Other cases, such as that of Lewis (1936), which shows that endocrine dystrophy can occur in only one of monozygotic twins, and those of Dennie (1924) and Penrose (1937), which show congenital syphilis in only one of such a pair, are also of clinical interest because they indicate the extremes of differential environmental effects which can occur even in the prenatal period. Hydrocephalic idiocy in one of two monozygotic twin brothers was described by Hinden (1956).

Twin study can further be used to indicate the possible effects of environment in the formation of character traits. Newman (1942) found that, between monozygotic twins, marked differences in temperament often developed and increased with age,

even when the twins were reared together. It is not impossible for psychosis to develop in only one of a pair of monozygotic twins, but this according to Smith (1929) and Rosanoff, Handy and Plesset (1935) is rare, Hobbs (1941), however, quotes several such cases. Since the diagnosis of defect, especially in the higher grade groups, depends upon social adjustment, these studies cannot be ignored in the search for causes of mental defect in the environment of early childhood. The investigation of cases of monozygotic twins reared apart enabled Newman (1942) to affirm that such pairs showed greater differences, both in mental ability and personality, than pairs reared in the same environments. A further question is the aetiological relationship between twinning itself and defects of all kinds. An association has been found which is especially noticeable in low grade defectives (Loof 1931, Berg and Kirmán 1960).

#### EVIDENCE FROM CHILDREN IN FOSTER HOMES

The effects of environment upon the intelligence levels and personalities of children not brought up in their own homes have been studied by Freeman, Holzinger and Mitchell (1928). A large number of children were examined. These were given intelligence tests before placement in foster homes and at various intervals subsequently. The new environment, from the point of view of educational opportunity as well as social training, was on the average an improvement upon the original home environment though the foster parents varied in intellectual and social level. The foster children showed a significant tendency to develop resemblance to the foster parents, both in mental level and in behaviour. The longer the period of adoption, the more marked was the change. The investigators concluded that improvement in environment increased the intelligence. In the whole group of 401 children, a correlation of +0.48 was obtained between intelligence and foster home rating. Pairs of unrelated children reared in the same foster home developed significant positive intercorrelations for intelligence. Also, the correlation between children and their foster parents on the Otis test scores was found to be +0.37. These results are of particular interest in the study of mental defect because many of the actual parents of the children placed in

foster homes were rated as feeble minded and even more were considered to be morally defective. In spite of this background, few cases of serious misbehaviour occurred in the foster homes. The significance of these findings would be very much diminished if there were reasons for supposing that more intelligent foster parents selected more intelligent foster children. The investigators admitted that this might have occurred, but not, they believed, to a sufficient extent to invalidate their conclusions.

Burks (1928) made a somewhat similar analysis of children in foster homes in California and again found significant correlations between foster child and foster parent (especially the mother) with respect to intelligence. Her conclusions were guarded but, after making a number of corrections, she asserted that 17 per cent of the variance of IQ was contributed by home environment and that an exceptionally good environment could raise the IQ rating of intelligence more than 20 points. A substantial reduction in mental defect in a community would be achieved if the general level of intelligence were even raised 5 or 10 points. Comprehensive claims for the beneficial effects on IQ of good home environment and education, especially at the infant school level, were made by Wellman (1945), but these have not been accepted as valid by critical authorities (Thomson 1947).

The converse analysis, of children adopted or fostered in similar environments, has also been made to find out whether, despite improvement of opportunities, differences in mental level remain, presumably because they are due to genetical causes. Lawrence (1932) tested illegitimate children in orphan ages and found significant relationship between intelligence of the child and occupational status of the father, even though most of the subjects had never had home environments of their own since the age of one year. In the extensive study of 800 children in orphanages, carried out by Carr Saunders and Jones (1927), a differentiation with respect to intelligence, corresponding to occupational class, was reported, but this differentiation tended to become obscured as length of time of residence increased.

Investigation of the problems of nature and nurture in children educated away from the usual family surroundings provides samples, which can be much larger and more homo-

geneous than are possible with twin studies. The method is less spectacular than twin analysis, but deserves to be used more widely. Both methods, however, have given results which show that the postnatal environment can contain decisive psychological factors tending to cause or prevent the development of mental defect.

## CHAPTER V

### FORMAL ANALYSIS IN HUMAN GENETICS

*General Principles—Association and Dissociation of Characters in the Same Person—Linkage—Gene Frequency—Deviations from Random Mating in Man—Parental Consanguinity Formula—Multifactorial Genetics in Man—Correlation Coefficients between Relatives of Different Degrees and Types—Assortative Mating—Mendelian Ratios—Birth Rank and Maternal Age*

#### GENERAL PRINCIPLES

THE understanding of the biological background of mental defect implies a knowledge of the formal principles of human genetics. In man, genetics is not an experimental science at the present time. Most of the relevant data are provided by circumstances outside the control of the investigator and their study forms a descriptive and inductive science with some resemblance to astronomy as opposed to experimental physics. Acquaintance with elementary biology and animal genetics is necessary but is not sufficient for the analysis of human genetical data. Special difficulties have to be met by special techniques not usually dealt with in biological text books. A descriptive outline of some methods which have proved useful in genetical analysis of mental defect, is therefore given in the present chapter.

In earlier chapters it has been emphasized that mental deficiency is not an inherited character in the ordinary sense. To obtain a true picture the various influences, recent and remote, which combine to produce the end result have to be separated from one another. The analysis can sometimes demonstrate the effects of a particular gene. In such cases the arithmetic of gene frequency can be applied with advantage. Quite commonly, although a disease can be attributed to a single gene, the gene is only a part cause of mental defect. In other patients the presence of a known hereditary condition may be incidental and unconnected with the mental changes.

## ASSOCIATION AND DISSOCIATION OF CHARACTERS IN THE SAME PERSON

Association of physical and mental defects is frequently found in hospital patients. The reason for this is not always genetical. A disability like blindness can be distributed evenly over the population, in so far as mental capacity is concerned, and yet, owing to the extra difficulties encountered by a disabled person in social and educational adjustment, the risk of such person's being diagnosed defective is accentuated.

Another extraneous cause of such a combination was emphasized by Pearson (1931). Both mental and physical disabilities and chronic diseases depress the social status of the individual, who is subject to them, and of his family. Owing to the tendency for mating to be confined within one social stratum, hereditary defects of several different kinds, especially those which are dominant, can be concentrated in the same individual or in different members of the same closely related group. This type of familial concentration is similar in principle to the concentration of genes in different localities, climates and societies, known as "racial" grouping. However, the assumption has been too often made that these processes lead to the formation of special "social problem" groups, reservoirs of defect and degeneracy in populations. Such theories cannot be justified in the absence of careful application of statistical genetical methods. To assume that such groups of genetical origin exist before these principles are applied is prejudicial to scientific enquiry.

In human genetics it is important to distinguish clearly between association of characters and genetical linkage. Since the concurrence of (or positive correlation between) two symptoms or traits can arise in a number of different ways, it is useful to examine methods of distinguishing the causes of such concurrence.

The first idea to examine is that two associated traits are manifestations of the same gene. This is called "pleiotropism" and is a well known phenomenon in experimental genetics. There are many steps between the chemical process, such as the formation of a particular enzyme, initiated by a gene and the final morphological or clinical result. Sometimes the inter-

relationship between pleiotropic effects can be ascertained by careful pathological investigations on experimental animals (Gruneberg, 1947). More often, no connection can be found other than the fact that the two symptoms, such as polydactyly and retinal degeneration tend to arise in the same individual. It is simpler to assume the existence of one gene rather than of two and the explanation of pleiotropism should always be first considered. For example, an abnormality, such as hereditary cataract which occurs in a case of mental defect, may be ultimately conditioned by the same gene as that which causes the defect. Manifestations of pleiotropism can be variable, in that the association of hereditary disease and mental symptoms may occur in one case but not in another, as, for example, in the hereditary ataxias.

In recent years much attention has been directed towards the association of certain types of disease with the ABO blood groups. It has been known for a long time that there is a statistical relationship between group A and malignant diseases (Kosambi, 1946). A consistent association has been observed between group O and duodenal ulceration (Roberts, 1959). Comparable investigations of conditions connected with mental deficiency have also been made. Analysis of blood group data in mongolism has not demonstrated significant association with any blood antigen (Lang Brown, Lawler and Penrose, 1953). However, Coffey and Jessop (1957) showed that anencephaly was especially common in the offspring of group O mothers.

Effects due to environment superficially resembling pleiotropism, can also give rise to positive correlations between characters. Thus, malnutrition can diminish body weight and also interfere with development of the teeth. Two such effects would be positively correlated in the general population and also within sibships. Concurrence of environmentally determined symptoms can also follow infection as, for example, when maternal rubella causes both cataract and heart defect in the foetus.

Instead of assuming only one gene to explain two associated traits, we can assume two genes to be acting. This does not prove that the two genes are genetically linked in the sense of being located together on one chromosome, as has been too



frequently assumed in the literature of human genetics. Several other types of association are possible. The social stratification of genes for various defects in a population, after the manner suggested by Pearson (1909), is statistically similar to geographical concentration of genes. Thus van Herwerden and Boele-Nyland (1930) noted a positive correlation between dark hair and blood antigen B in the general population of Holland and attributed this to uneven geographical grouping. Similarly, in a mixed population of Africans and Europeans, the *Rhesus* blood group cDe would be correlated with dark skin colour. The ultimate test to distinguish between pleiotropism and stratification is to examine sibships. If stratification, or its equivalent, is solely responsible for an association of traits in a sample of unrelated individuals, the correlation will disappear within the sibship because there the parental types are fixed.

Less attention has been paid to the dissociation of characters than to their association. Two characters can, however, tend to be negatively correlated. This may happen if they are physiologically compensatory, like length and breadth of the head among people of equal cranial capacity. More interesting, genetically, is the behaviour of two dominant allelic genes. The presence of one precludes the presence of the other on the same chromosome. Thus, there is a slight negative correlation between their effects if they are separately dominant, like the A and B blood antigens. The fact that blood group AB is found to be much less frequent than it should be in the general population, on the assumption that both A and B are quite independently assorted, is, in itself, strong evidence in favour

TABLE XIX  
ASSOCIATION, DISSOCIATION AND LINKAGE

Cause of Relationship between Two Genetical Characters	Direction of Association	
	In General Population	Within the Sibship
Same gene (pleiotropy)	+	+
Geographical grouping	+	0
Allelic genes (same locus)	-	-
Linked genes (neighbouring loci)	0	+ or -

of their being due to allelic genes Table XIX summarizes these points concerning association and dissociation

### LINKAGE

Ordinary genetical linkage of two genes that is proximity of their loci on a chromosome does not cause association of the characters which they determine in a population of unrelated individuals. Within a sibship or within a group of collateral relatives, it produces either an association or a dissociation according to whether the two genes concerned are in the phase of coupling (association) or of repulsion (dissociation). Both phases are equally frequent in ordinary circumstances with random mating. If two rare recessive traits were the results of closely linked genes however, the coupling phase would cause their association in sibships with consanguineous parents (Haldane, 1950) but the repulsion phase would not be noticeable.

The mistake is often made of supposing that the genes which determine two characters appearing simultaneously in certain members of a sibship are necessarily linked. This error can be avoided by realizing the necessity of demonstrating the complementary picture of the same two characters in repulsion in another sibship. If blue eyes and fair hair were assumed to be genetically linked then we should be able to collect sibships in which the traits were associated. However there would also be sibships in which the traits were dissociated where those sibs who had blue eyes had dark hair and those who had brown eyes had fair hair. The analysis of genetical linkage involves difficult mathematical problems. Several certain linkages are known in man. The first established was that between the genes for colour blindness and haemophilia on the X chromosome. Linkage between two definite autosomal traits was first proved for elliptocytosis and the Rh antigen system (Lawler, 1954).

The special condition of very close linkage of genes with similar effects at one complex locus, believed by Fisher to account for the behaviour of the Rh complex (Race, 1944), may be a usual genetical phenomenon. However, crossing over in such systems is so rare that close linkage of this type cannot be distinguished from one locus with multiple alleles in ordinary work on human pedigrees.

## GENE FREQUENCY

The concept of gene frequency is of fundamental importance in the genetics of wild populations, which human populations resemble much more closely than selected breeds of laboratory animals. The idea is essential to the mathematical study of evolution because many of the processes of natural selection can be expressed in terms of progressive increase or decrease in gene frequencies. In the shorter term problems of human populations, the concept is also indispensable. The elementary theoretical results were discovered independently by Hardy, Pearson and Weinberg.

Let us suppose that the frequency of a given gene,  $A$ , in the general population is represented by  $p$ . Further, let the frequency of the allelic partner gene,  $a$ , be  $1-p$ . Every chromosome is represented twice in each person, so that three types of individual are possible. There are (i)  $AA$ , those homozygous for  $A$ , (ii)  $Aa$ , those heterozygous for both  $A$  and  $a$ , and (iii)  $aa$ , those homozygous for  $a$ . The frequencies of these three classes in a system of random mating will be  $p^2$ ,  $2p(1-p)$  and  $(1-p)^2$ , respectively. If the gene  $a$  is infrequent as compared with gene  $A$ , class (ii) will be much more numerous than class (iii). Thus, if  $p = \frac{9}{10}$ , the relative numbers in the three classes are as 81 : 18 : 1.

It can be easily appreciated that in the case of a rare recessive defect, whose genotype is represented as  $aa$ , the heterozygous carriers of type  $Aa$  will be much more prevalent than the people actually showing the disease. If, as Goddard (1914) suggested, all mental defect were due to a single recessive gene  $a$ , the type  $aa$  must have a frequency in the community of about 2.56 per cent (see Table IX). The frequency of gene  $a$  would thus be  $\sqrt{0.0256} = 0.16$ . Hence, the relative numbers of the three types  $AA$  (normal),  $Aa$  (normal but carrier of defect) and  $aa$  (defective), if mating in the general population were at random, would be

70.56 : 26.88 : 2.56

More than a quarter of the population would be carriers, a much greater proportion than the 10 per cent supposed to constitute the social problem group.

An important consequence of random mating is that, under its influence, the proportions of the genotypes to one another

however, is demonstrated here, namely, that the rarer a recessive condition, the fewer instances will there be of affected parents. Indeed, the proportion of cases with affected parents is the same as the gene frequency ( $q$ ). Hence, in rare recessively determined diseases, that is where  $q=1/100$  or less, the random mating table can still be almost correct even if all affected individuals are infertile.

#### DEVIATIONS FROM RANDOM MATING IN MAN

If the mating system in the population studied is not random, gene frequency calculations may require considerable adjustment. In human populations there are two common kinds of departure from random mating, due respectively to (i) inbreeding, and (ii) assortation. Both processes tend to increase the frequency of homozygotes in the population. The first has special significance in relation to recessive inheritance and will be discussed immediately. The second, assortative mating, will be considered later.

Inbreeding in man is limited by laws and customs, and commonly the closest type of union is that between first cousins. In some communities incest occurs (see p. 62), while in others even first-cousin marriages are considered abnormally consanguineous. All human communities which have been subject to genetical observation contain cousin marriages in excess of random expectation and thus show a definite tendency towards inbreeding.

It has been known for a long time, and commented upon by Darwin (1868), that parental inbreeding probably favours the appearance of certain congenital defects in the offspring. Garrod (1902), however, after discussion with Bateson, was the first to describe the mechanism. Alkaptonuria, an extremely rare abnormality, was found to arise from consanguineous unions in more than half the known cases. It was pointed out that a very rare gene could only easily occur in both parents if they had a common ancestor. In this way the observations, that defects such as the deaf mutism observed by Boudin (1862) were associated with inbreeding, could be given a clear biological interpretation. On analysis of the gene frequencies involved, it becomes plain that only in rare recessive diseases—the rarer the better from this point of view—is consanguinity of signifi-

cance The simplest formula relating gene frequency to parental consanguinity was explicitly given by Lenz (1919)

#### PARENTAL CONSANGUINITY FORMULA

The following argument only applies to recessively determined diseases whose frequency in the general population is less than one in 1000 and preferably less than one in 10,000 and which occur in populations where close inbreeding is uncommon Call the frequency of first-cousin unions, in the general population  $\alpha$ , this quantity will vary in most communities under consideration between  $\frac{1}{2}$  and 2 per cent

Let the three genotypes be represented thus

Genotype	Phenotype	Frequency
$BB$	Normal homozygote	$p^2$
$Bb$	Normal heterozygote	$2pq$
$bb$	Affected homozygote	$q^2$

where  $p + q = 1$  and  $q$  is, say,  $1/100$

Now, in the limiting case where the frequency  $q$  approaches zero, every relevant family showing affected homozygous offspring  $bb$ , is derived from a pair of normal heterozygous parents  $Bb$  Consider, therefore, the case of a given heterozygous individual,  $M$  The chance that he will mate with a first cousin is  $\alpha$ , and the chance that he will *not* mate with a first cousin is  $1 - \alpha$  or, for practical purposes, unity

The chance that  $M$ 's first cousin will be heterozygous for the rare gene,  $b$ , is  $1/8$  (see Table XXIII) so that the chance that  $M$  mates with a heterozygous first cousin is  $\alpha \times \frac{1}{8}$  Now, if  $M$  mates with an unrelated person, the chance that his mate will be heterozygous is  $2pq$ , or, for practical purposes,  $2q$ , since  $p$  is very nearly equal to unity

The total chance of mating with a heterozygote is, therefore,  $\frac{\alpha}{8} + 2pq(1 - \alpha)$ , that is nearly  $\frac{\alpha}{8} + 2q$  Hence, the frequency,  $F$ , of first cousin unions among all matings which can give rise to defective homozygous offspring must be

$$F = \left( \frac{\alpha}{8} \right) / \left( \frac{\alpha}{8} + 2q \right) = \frac{\alpha}{\alpha + 16q}$$

(see Appendix 5) In making an expected estimate of  $F$  from

an observed frequency ( $q^2$ ) of known cases of a recessive condition, cases known to have consanguineous parents should be excluded

An increase in the amount of inbreeding effectively increases the incidence of a rare recessive defect but causes little change in the incidence of a common recessive character. Consequently, the incidence of a rare disease of recessive origin fluctuates from time to time and from place to place according to the amount of inbreeding in the community concerned. Haldane and Moshinsky (1939) pointed out that a reduction in the number of cases of rare recessive defects is likely to be taking place at the present time in European communities because inbreeding is becoming less frequent. The gene frequencies corresponding to each condition, however, are not appreciably changed.

#### MULTIFACTORIAL GENETICS IN MAN

Much attention is paid in all books dealing with human genetics to dominant, recessive and sex-linked types of inheritance. These can be strikingly demonstrated in pedigree studies. Actually the type of inheritance most commonly observed in human genetical material is due to the combined actions of more than one gene. Indeed, the number of genes involved can be very large. The genetical basis of characters, whether physical, like stature, head size and cephalic index, or mental, like intelligence level, specific ability or temperament, is mainly multifactorial. Usually, numerous environmental influences also contribute. It seems therefore worth while to devote some space to the discussion of the theory of this branch of human genetics, in which one of the earliest established techniques of genetical analysis is used.

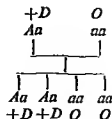
Galton (1889) published the results of his observations on family likeness and individual variation in respect of stature in man. He observed that if sets of paired measurements of related persons were plotted against one another, the degree of familial likeness could be estimated. The method was to take a group of men of the same stature and to find, for example, the mean stature of their brothers. Thus, the mean stature of brothers of men 72.2 inches tall was found to be 70.3, whereas the mean stature of all men in the general

population was 68.2 inches. On the average, the brothers stood about halfway between the level of the originally specified group of men and the normal level of the population. In general, if the deviation from the population mean of a given man is  $D_1$  inches and the mean value of the deviation, from the same origin, of his brothers is  $D_2$  inches,

$$\frac{D_2}{D_1} = r', \text{ or the regression coefficient}$$

In such a case as this, where the distribution is symmetrical because it is immaterial which brother is taken first,  $r'$  is equal to the correlation coefficient. Substituting,  $D_2 = 70.3 - 68.2 = 2.1$  and  $D_1 = 72.2 - 68.2 = 4.0$ , the value,  $r = 2.1/4.0 = 0.502$ , is obtained. In actual practice the series of mean values of brothers' statures will not lie perfectly upon a straight line on a scatter diagram and the regression coefficient has to be calculated by finding the covariance and variance. When the table is symmetrical, as with brother-brother pairs, the correlation coefficient—the product moment coefficient of Pearson and Bravais—is identical with the regression coefficient because the variances of the two compared groups are equal. In the more general case, where, say, parents and children are studied, there are two regression coefficients differing from one another by virtue of the different variances of the two classes compared, the correlation coefficient is then the geometric mean between the two regression coefficients.

The genetical background of the regression or correlation value of  $\frac{1}{2}$ , which was so frequently found by Pearson in comparisons of measurements of pairs of sibs or of parents and children, is extremely simple. Let the gene  $A$  be responsible for a quantitative alteration in a metrical character by the amount  $+D$ . Should a parent have such a gene, his stature will be  $+D$  above the normal, assuming that the allelic gene  $a$  which he carries is neutral in this respect. Suppose the other parent has average stature, neutral genes and zero deviation. The parent whose genotype is  $Aa$  will transmit the gene  $A$  to half the offspring. Hence the average deviation from the normal in the stature of his offspring will be  $+D/2$ , as can be seen in the chart.



Similarly, half the brothers or sisters of a propositus of type  $Aa$  with deviation  $+D$  will have deviations  $+D$ , thus, the mean stature deviation of the sibs will be  $+D/2$ . The regression coefficient again is  $(+D/2) - (+D) = \frac{1}{2}$ .

The fraction,  $\frac{1}{2}$ , which measures the correlations of many metrical characters in parent child and sib pairs, is a direct consequence of the fact that a parent transmits to each offspring half of his genic material. This is only strictly true of autosomal genes. In the case of sex-linked genes, when sex of parent and child is specified, the situation is different.

It is easy to see that this argument can be extended to any degree of relationship. If a grandparent has a gene causing the deviation  $+D$ , one quarter of his grandchildren will have it. Their mean measurement will be  $+D/4$  and the regression coefficient, or measure of likeness, is  $\frac{1}{4}$ . In general terms, the degree of hereditary likeness between the two relatives depends inversely upon the number of steps in the relationship, as shown in the following table.

TABLE XXIII  
DEGREE OF HEREDITARY LIKENESS

Type of Relationship to Propositus	Number of Steps in Relationship	Degree of Hereditary Likeness i.e. probability that the relative carries the same gene
Sib parent, child	1	$\frac{1}{2}$
Half sib, uncle, aunt nephew niece, grandparent grand child	2	$\frac{1}{4}$
First cousin great uncle, great nephew great grandparent, great grandchild	3	$\frac{1}{8}$
First cousin once removed	4	$\frac{1}{16}$
Second cousin	5	$\frac{1}{32}$
General case	$n$	$1/2^n$



The observed degree of phenotypical likeness is only the same as the probability of having the same gene as the *propositus* if each gene has its full effect independently of all other factors. In reality the effects of genes can be hidden on account of their recessivity, through modification by other genes or by environmental influences. These factors usually diminish familial likeness of related persons, but if there is an environment which modifies members of family groups all in the same sense, then apparent likeness is increased.

#### CORRELATION COEFFICIENTS BETWEEN RELATIVES OF DIFFERENT DEGREES AND TYPES

The theoretical correlation coefficients between relatives for hereditary characters can be derived from distributions of parents and offspring as in Table XX. In the standard case we assume that each gene asserts its effects independently and that such effects are precisely additive (Fisher, 1918). Thus, the gene *A*, present in homozygous form *AA* will be supposed to exert just twice as much effect as when it is present in heterozygous form *Aa*. The same applies to the effect of allele *a*. On this assumption the correlation between parent and child can be shown to be exactly  $\frac{1}{2}$ , irrespective of the gene frequency. The same result follows for pairs of sibs and the distributions for these two cases are given in Appendix 6. The argument can be extended to cover any degree of relationship and the correlation coefficients, worked out by this method, are the same as the degrees of hereditary likeness given in Table XXIII. Sometimes the average measurement of the two parents (Galton's mid-parental measurement) is tabulated against measurement in the child. In this case the expected coefficient is  $1/\sqrt{2}$ , or 0.71, when perfectly additive hereditary factors are the sole causes of variation.

If, instead of dealing with one pair of genes, we considered a set of three or more additive allelic genes, the resulting correlations would be unaltered. They would also be unaltered if we took a series of several gene pairs at different loci, *A* and *a*, *B* and *b*, *C* and *c*, etc., provided that all combinations were perfectly additive.

The result is altered when genes are not perfectly additive. The standard exception occurs when one gene is completely

recessive to another, e.g. the types  $AA$  and  $Aa$  are equivalent but both differ quantitatively from the type  $aa$ . In the case of dominant or recessive genes, the correlations are all reduced but the amount of reduction depends upon the gene frequency

The parent-child correlation becomes  $\frac{q}{1+q}$  and that for sibs

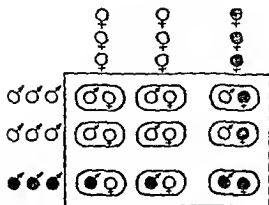
$\frac{1+3q}{4(1+q)}$ . For a rare dominant character ( $q \rightarrow 1$ ), the reduction

is very slight. With a rare recessive character ( $q \rightarrow 0$ ), however, the parent-child correlation coefficient approaches zero and the sib-sib correlation approaches  $\frac{1}{4}$ . For common genes, e.g. when  $p=q=\frac{1}{2}$ , the parent-child coefficient becomes  $\frac{1}{3}$  and the sib-sib coefficient  $\frac{5}{16}$ .

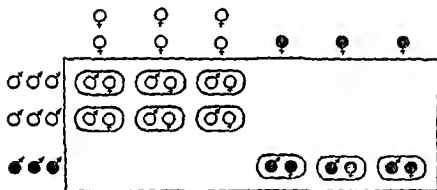
The theory of correlation as a measurement of hereditary likeness was extended by Hogben (1932) to include the effects of sex-linked characters. In the female there are three types, which can be assumed in the general case to be the results of perfectly additive genes, tables can be worked out for every degree of relationship. The overall correlations for parent-child and for sib-sib pairs are still  $\frac{1}{2}$ , as with autosomal additive characters, but they differ when sexes are specified (Maynard-Smith, Penrose and Smith 1961). Thus, with sex-linked genes the father-son correlation is zero, those for father-daughter and for mother-son,  $1/\sqrt{2}$  or 0.71, and that for mother-daughter,  $\frac{1}{2}$ . Brother and brother show a correlation of  $\frac{1}{2}$ , brother and sister,  $1/2\sqrt{2}$  or 0.35, and sister and sister,  $\frac{3}{4}$ . The coefficients, which apply to pairs one or both of whose members are females, are reduced if the sex-linked character under consideration is recessive. Examination of correlations between relatives for traces of this pattern may be used as a test for the presence or absence of the effects of sex-linked genes in metrical family data.

#### ASSORTATIVE MATING

As previously mentioned, there are processes other than inbreeding that cause departures from random mating. In human populations tendencies have been observed for people to choose partners resembling themselves in one or more characteristics. This can be termed phenotypical assortment.



1. RANDOM MATING



2. PERFECTLY ASSORTATIVE MATING

Figure 6.—Diagrammatic representation of contrast between random and perfectly assortative mating.

A population of six males and six females of one type (light circles) and three males and three females of another type (dark circles) is represented in each section. Among the randomly mated pairs (1) the correlation for type is zero but among the perfectly assorted pairs (2) it is unity.

Thus, in North America, people with light-coloured skin tend to mate with one another and the same holds good for people with dark skin. Less noticeable, but significant, is the tendency for the fair and dark complexioned in European communities to mate with one another (see Figure 6).

Degrees of assortment can be measured conveniently by correlation coefficients estimating similarity of husband and

wife with respect to any trait Pope and Pearson (1908) estimated the likeness of husband and wife pairs in respect of physical traits, such as eye colour, stature and general physique, in this way and found positive correlation values of the order of 0.2 and 0.25 for most of them. Davenport's (1917) extensive data on stature correspond with an interparental coefficient of 0.33. Mental traits have also been studied and positive values have been found indicating tendencies for persons of like temperaments to mate (Penrose 1944). The likeness between husband and wife with respect to intelligence level has been shown to be very strong; it seems to be represented by a coefficient of the order of 0.5.

If physical or mental measurements are assumed to represent the effects of perfectly additive genes, assortive mating in the parents gives rise to precisely predictable alterations in the likeness between parents and children, sibs and other related pairs. Positive assortation in parents increases all measurements of hereditary likeness (Stanton 1946). Also if the same degree of assortation continues for many generations, a state of equilibrium is approached in which the new values of the degrees of hereditary likeness are dependent in a simple manner upon the degree of parental assortation. Then if the interparental likeness is measured by the correlation coefficient,  $m$ , the parent-child and sib-sib coefficients become  $\frac{1+m}{2}$ . The mid-parent and child coefficient is raised to  $\sqrt{\frac{1+m}{2}}$ .

Thus, if  $m=1$ , as is the case with interparental intellectual stature, the expected parent-child and sib correlations are both raised to  $\frac{1}{2}$  and the mid-parent and child coefficient is raised to  $\sqrt{\frac{1}{2}}$ , or 0.87. We can learn from consideration of various factors—(a) those which tend to diminish likeness between relatives, such as dominance and recessivity, and (b) those which raise the likeness, such as assortative mating—that the observed values of correlation coefficients intended to measure the influence of hereditary factors must be interpreted with considerable caution.

#### MENDELIAN RATIOS

Although the ultimate confirmation of any hypothesis of a

single gene as the cause of a defect depends upon finding a Mendelian ratio among the offspring in relevant families, conditions suitable for crucial testing are not found often in human data. In the case of a rare dominant abnormality, where there is always full manifestation, the normals and abnormal will be represented in the ratio of 1 : 1 among the pooled offspring of affected individuals. With recessive conditions the position is less favourable owing to the fact that, unless at least one child in a sibship is affected, the sibship will not be recorded. Although the expected Mendelian ratio of normal to abnormal is 3 : 1, in small sibships there will be too few normals actually recorded. In fact, when the number of sibs is  $S$ , the ratio, expected normal to expected abnormal, is  $3[1-(\frac{1}{4})^{S-1}] : 1$ . Thus, if the size of the sibship is 4, the ratio of normal to abnormal will be nearly 2 : 1; and this is about

TABLE XXIV

FACTORIAL METHOD OF TESTING RECESSIVE HYPOTHESIS ON SIBSHIPS CONTAINING CASES OF PHENYLKETONURIA (MUIRO, 1947)

Size of Sibship, $S$	No of Sibships of size $S$ , $N_s$	Total No of sibs $S N_s$	Number of Sibs Phenylketonuric		Variance of expected number,* $N_s K_f$
			Observed	Expected $S N_s / 4 [1 - (\frac{1}{4})^S]$	
1	6	6	6	6.00	0.00
2	7	14	8	8.00	0.86
3	6	18	10	7.78	1.58
4	5	20	8	7.31	2.10
5	7	35	13	11.47	4.14
6	5	30	12	9.12	3.88
7	2	14	4	4.04	1.94
8	3	24	8	6.67	3.52
9	1	9	2	2.43	1.38
10	2	20	5	5.30	3.18
11	1	11	2	2.87	1.81
12	1	12	3	3.10	2.02
13	1	13	4	3.33	2.23
Total	47	226	85	77.42	28.64

Out of 226 sibs, altogether 85 were affected against 77.42, the expected number on the recessive hypothesis. The difference between the observed and expected values here is 7.58, which is slightly but not significantly greater than the standard error,  $\sqrt{28.64}$ , or 5.35.

\*See Appendix 7.

the value commonly found in human data on recessively determined rare conditions

For precise estimation the modified expected number of affected children can be calculated in each sibship containing a recessively determined defect. Expected and observed numbers can be added up over a series of sibships and compared. This method has been specially advocated by Hogben (1931b), who has provided tables of expectations and their standard sampling variances for sibships of each size. An example is given in Table XXIV, where the agreement between observation and expectation, on the hypothesis of a true 3 : 1 ratio, is satisfactory. A more refined method of wider application has been devised by Haldane (1932b), by means of which the most probably true ratio of affected to normal can be estimated. The choice of method should depend upon the manner in which data are collected (Haldane 1938b). In data from medical literature the precise influence of sampling is often very difficult to determine, because families containing a large number of affected members are likely to be noticed while isolated cases with "negative family history" may remain unrecorded.

#### BIRTH RANK AND MATERNAL AGE

In sibships which contain affected members, tests can be made for environmental agencies, and in particular, for the effects of maternal environment. Abnormal offspring may be found to occur unduly frequently either in the first born children or in children whose births are preceded by exceptionally large numbers of pregnancies. Also the age of the mother or of the father can be aetiologically important. By far the simplest method of testing such hypotheses is the comparison of data on the cases of the abnormality in question with general population statistics. There are two difficulties, however, first, that the effects of birth order and parental age are closely related and may be awkward to disentangle, though we can ascertain which effect is the more significant. Secondly fully adequate general population statistics are not often available, they never record the birth ranks of stillbirths and miscarriages. When they are unsatisfactory, a control group has to be built up from the internal evidence of the data on the families containing abnormals. Thus, in a sibship of size  $S$  containing  $d$

defectives and no sibs of unascertained status, the random chance that the first birth (or any other specified birth) results in a defective is  $d/S$ . When a series of sibships is available, the expectations in each birth rank, for all sibships, are summed and the distribution of the expectation totals compared with the observed totals. Sibships in which all the known members are affected give no information.

The method can easily be used for comparing expected and

TABLE XXV

OBSERVED AND EXPECTED NUMBERS IN EACH BIRTH RANK AND MATERNAL AGE GROUP IN SIBSHIPS CONTAINING 121 CASES OF ANENCEPHALY, HYDROCEPHALY OR SPINA BIFIDA (Pentose 1946)

Birth Rank	Maternal Age								Total
	15-19	20-24	25-29	30-34	35-39	40-44	45-49		
1	1 0 93	11 14 22	13 9 21	5 3 00	1 0 83	—	—	31 28 19	
2	— 0 08	5 7 75	6 10 96	3 9 16	1 1 83	—	—	15 29 78	
3	—	2 2 49	6 6 71	6 7 03	4 2 80	—	—	18 19 36	
4	—	1 0 44	2 4 78	3 3 73	5 2 67	1 0 50	—	12 12 12	
5	—	1 0 12	2 2 77	2 2 56	8 5 17	2 0 73	—	15 11 35	
6	—	—	—	1 1 06	2 2 23	1 0 40	—	4 5 48	
7	—	—	—	1 0 42	2 1 92	2 1 17	—	5 4 84	
8	—	—	—	3 1 31	5 1 57	1 1 09	2 0 54	11 4 51	
9	—	—	—	1 0 51	1 1 03	2 0 86	—	4 2 40	
10	—	—	—	— 0 40	1 0 47	2 0 38	1 0 09	4 1 34	
11	—	—	—	—	1 0 27	—	—	1 0 57	
12	—	—	—	—	— 0 09	1 0 25	—	1 0 34	
13	—	—	—	—	—	—	—	—	
14	—	—	—	—	—	0 35	—	0 35	
15	—	—	—	—	—	0 20	0 08	0 28	
							0 09	0 09	
Total	1 1 01	20 25 02	29 35 91	25 31 85	31 19 85	12 6 56	3 0 80	121 121 00	

TABLE XXV—*continued*

Number of Cases	Mean Birth Rank		Mean Maternal Age in Years	
	Observed	Expected ±S D	Observed	Expected ±S D
121	4 00	3 38±2 44	31 69	29 77±5 94

Difference between Observed and Expected Mean Values		Standard Error
Birth rank	+0 62	$\pm \sqrt{\frac{2.44}{120}}$ , i.e. ±0 22 (ranks)
Maternal age	+1 92	$\pm \sqrt{\frac{5.94}{120}}$ , i.e. ±0 54 (years)

observed numbers of cases in different maternal or paternal age groups Table XXV shows an example of such a calculation, based upon 111 sibships each containing one case of foetal deformity of specified type and 10 sibships each containing two such cases. Every sibship's contribution, in the table, included at least one sib known not to have any of the deformities in question. If two sibs fell within the same age group, their expectations were added together. The expected and observed values in such tables can sometimes conveniently be compared by the  $\chi^2$  test. In this instance, the means and standard deviations of the distributions of the expectation totals were calculated and used for a comparison with observed values. For both measurements, birth rank and maternal age, the means for the abnormals are significantly greater than would be expected. The discrepancy between mean observed and mean expected maternal age, which represents a tendency for older mothers to have malformed offspring, is small but significant. The difference, +1 92 years, is 3 56 times its standard sampling error. For birth order, the corresponding difference, +0 62 ranks, is only 2 78 times its standard error. Inspection, however, shows that this difference might have been more marked but for a tendency for first born children to be malformed. The strong correspondence which exists between birth rank and maternal age makes it difficult to ascertain the full independent effects of the two variables unless further



refinements of statistical technique are introduced. Similar problems arise in relation to paternal age. This variable is closely correlated with both the others. If data on both fathers' and mothers' ages are available their relative effects can be isolated statistically by partial correlation (see page 209). The method can be applied to the separation of them both from birth order if all relevant information is tabulated.

## CHAPTER VI

### THE GENETICS OF INTELLIGENCE

*Inheritance of Intelligence—Inheritance of Social Ability—Intelligence Levels of Parents and Sibs of Defective Patients—Correlations between Relatives—Regressions—Threat of Decline in Intelligence Level—Equilibrium of Intelligence and Fertility*

#### INHERITANCE OF INTELLIGENCE

THE chief predisposing cause of social failure in early life is low intelligence level. Intelligence, measured by any known test, is a graded character and it resembles other quantitative measurements, such as stature. From the point of view of genetics it is not a simple character. It does not usually segregate and it is the result of the combined action of a great number of genes and environmental influences.

Each different mental test measures a different aspect of intelligence, just as measurements of stature, span or girth measure different aspects of body size. All scholastic intelligence tests are closely related to one another and they are also related, less intimately but significantly, to non-verbal and performance tests. Thus, success or failure by one standard predicts, to some extent, success or failure on another test.

The results of tests in general use agree quite well with estimates of intelligence, which could be inferred from qualitative examinations of people and expressed perhaps in terms of rating scales. Some tests are more accurately constructed or are inherently more reliable than others, but the most reliable are not necessarily the best measurements of the fictitious quantity, which represents what is commonly implied by the term intelligence. It might be a good plan to study separately the genetics of each type of test performance, e.g. verbal and non-verbal, if accurate scientific results were desired. Tryon (1929), for example, was able to give a convincing demonstration, with rats, of the genetical principles of ability to traverse mazes. The

inheritance of this particular ability was evidently multifactorial

#### INHERITANCE OF SOCIAL ABILITY

In view of the acknowledged definition of mental defect as social failure, the most logical method of studying its inheritance is to examine the genetics of social failure directly. This has been attempted by Doll (1937). A scale was devised for measuring social ability, expressed, unnecessarily, in the form of a "social quotient" by rating accomplishments pertaining to social maturity. Doll examined a number of families and estimated the degree of social maturity of each member. He concluded that the social quotient level might be largely an inherited character. The mid parent and child correlation coefficient was 0.75. A very high degree of assortative mating, with respect to social maturity, was evident in these families. The expected value of the mid parent child coefficient, on the assumption of additive gene inheritance, would thus be exceptionally high (above 0.9). The observed value is too low to agree with an additive gene hypothesis.

Measurements of the social quotient correlate closely with Binet scores, but the home and cultural environment probably has even more effect on the social rating than upon Binet test results. Social maturity has many dimensions and is not a character that naturally lends itself to genetical analysis.

#### INTELLIGENCE LEVELS OF PARENTS AND SIBS OF DEFECTIVE PATIENTS

Data available for the study of the inheritance of intelligence can be obtained from examination of the sibs and parents of known cases of defect. The simplest plan is to exclude the patient, that is the propositus, from the sibship. If the patient is young, it may be possible to test sibs and obtain measurements of their mental abilities, but in very few cases will it be possible to do this with parents. Mental tests are not, as a rule, accurately standardized for application to people at all ages, though Wechsler's scale for adults may ultimately meet this need. In the parent-child relationship, comparison of adult and child test achievement is of questionable validity and rating scales often have to be relied upon for assessment of mental capacity. The figures given in Table XXVI were obtained in the

TABLE XXVI

MENTAL GRADES OF PARENTS AND SIBS OF 1148 PATIENTS

Grades of Parents		Patients and Sibs Number in each Grade					
		S	N	D	F	Imbecile	Idiot
		Superior	Normal or Average	Dull or Borderline	Feeble minded		
S × S	{ Patients Sibs	— —	— —	— —	— —	1 —	— —
S × N	{ Patients Sibs	— 8	— 15	1 —	3 —	2 —	3 —
N × N	{ Patients Sibs	— 59	— 2753	100 174	216 56	303 47	178 23
N × D	{ Patients Sibs	— 1	— 552	40 173	86 79	51 28	19 12
N × F or D × D	{ Patients Sibs	— —	— 196	11 97	62 65	26 17	14 9
N × Imbecile or D × F	{ Patients Sibs	— —	— 60	6 33	32 39	13 13	3 5
D × Imbecile or F × F	{ Patients Sibs	— —	— 17	2 11	9 28	12 9	1 1

Colchester Survey (1938) from the families of 1,148 patients, whose parents were known well enough to be rated with confidence for mental ability. The tendency for the general average level of the sibs to follow the average grade of the parents is clearly shown. Comparison with test results indicated that the difference between any two of the adjacent ratings was approximately equivalent to 22 points of Stanford-Binet intelligence quotient. On this basis, equating *S* with 122, *N* with 100, etc., the mean levels of parent and child intelligence can be directly compared, giving the results shown in Table XXVII.

The mean level of the sibs drops regularly as the mean intelligence level of the parents descends, though, perhaps because of errors in classifying parents, the sib level drops more slowly. If perfectly additive genes were wholly responsible for grades of intelligence, the means for parents and children

TABLE XXVII

ESTIMATED MEAN MENTAL RATIOS OF PARENTS, SIBS  
AND PATIENTS

Type of Mating	Parents	Sibs of Patients	Patients
S×S .	122	—	34 0
S×N .	111	107 6	38·9
N×N .	100	96 7	37 4
N×D .	89	88 11	50 5
N×F or D×D	78	82 0	49 4
N×Imbecile or D×F	67	75 1	50 7
D×Imbecile or F×F . . .	56	67 3	45 0

S=122

F=56

N=100

Imbecile=34

D= 78

Idiot=12

should always agree. The fact that the means for the sibs of patients are somewhat higher than the means for the parents, when the parents are in the defective range, suggests that some of the genetic factors producing defect of this magnitude are heterozygous. A similar explanation might be put forward to account for two children with intelligence close to the normal level who were derived from a mating of brother and sister (Penrose 1934a). On the other hand, a large proportion of the offspring of unions of parents who are both in the defective class are lost sight of through death in early infancy. Among the sibs of the patients, in the lowest row of Table XXVI, were 25 (not rated) who died in early infancy as against 66 of known mental grade. For the whole sample of 1,280 patients in the same survey, the deaths in infancy numbered 906 against 4,645 sibs of classified mental grade; this would correspond to 12·9 for a sample of 66 classified sibs. Possibly the increased infantile mortality rate among the offspring of very dull or defective parents is due to the occurrence of cases of low-grade defect which, if they had not died and thus escaped classification, would have lowered the mean level of the sibs in a marked manner (as in Figure 4).

An important feature of the material summarized in Tables

XXVI and XXVII is the noticeable tendency for the grade of patient to have an inverse correspondence with the grade of the parent. When the parents have normal mental capacity, there is clear segregation between the patients and their relatives. In the families where parental abilities are subnormal, the distinction is lessened, the patients are higher and the sibs lower. This is merely a further illustration of the circumstances discussed in Chapter III, namely that the patients fall mainly into two biological groups, the low grade infertile cases, and the high grade fertile cases which are capable of transmitting genes tending to cause low scholastic capacity to their children.

#### CORRELATIONS BETWEEN RELATIVES

The most formal approach to the problem of inheritance of intelligence utilizes the correlation technique. To obtain reliable results, the families selected should be a random sample of the general population. Unfortunately few surveys with accurate testing and careful sampling have ever been made. Some of the most interesting results of measurements of likeness in mental ability are summarized in Table XXVIII. Information about the parent and child relationship is particularly scanty. The important estimates of Willoughby (1928) and Jones (1928) differ considerably, though both were made on random samples. The true value of this correlation coefficient is not necessarily as high as 0.5, though it is often assumed that the likeness for intelligence must be the same as that found for stature of parents and children by Pearson and Lee (1903).

Estimates for sib pairs can be obtained from data on school children. Numerous surveys have been undertaken with variable results, according to the tests used and the methods of sampling. The careful survey of Roberts (1940) gave a value of 0.54 for the sib-sib coefficient. Thorndike's measurement was higher than this, but most other surveys have given lower values. Again, it cannot be assumed that the sib-sib likeness for intelligence is necessarily correctly expressed by the correlation of 0.5. Even if repeated surveys should give values centring round this figure, the interpretation is difficult. A certain amount of the likeness of sibs must be attributed to similar surroundings, in the family and in the home. The real coefficients—which measure purely genetical effects—are possibly all

TABLE XXVIII  
CORRELATION COEFFICIENTS FOR INTELLIGENCE

Source	Type of Related Pairs		
	Parent-Child	Sib-Sib	Parent-Parent
Burt (1946)	0.34*	0.48	—
Thorndike (1928)	—	0.60	—
Willoughby (1928)	0.35	0.42	0.44
Jones (1928)	0.53	0.49	0.60
Herrmann <i>et al</i> (1933)	—	0.32	—
Matthews <i>et al</i> (1937)	—	0.30	—
Penrose (1938)	—	—	0.39
Cattell <i>et al</i> (1938)	0.84	0.77	0.81
Roberts (1940)	—	0.54	—
Halperin (1945, 1946)	0.37	—	0.65
Alstrom (1961)	0.54 } 0.55 }	0.47 } 0.58 }	0.50

\*Estimated from parental occupations.

somewhat lower than those observed. Moreover, dominance and recessivity of the component genetical factors may lower the expected values, as already pointed out in Chapter V.

A most important factor to consider is the inter-parental correlation because, for intelligence, this is probably very large; it is evidently of the order of 0.5. The effect of this is to raise by 50 per cent whatever expected correlations we may assume to be reasonable on genetical grounds with random mating. If perfectly additive factors were responsible for intelligence level, the coefficients for parent-child and sib pairs should be 0.75 each, and such values have only been obtained in selected samples, like that of Cattell and Willson (1938). It seems safe to conclude from the study of these coefficients, as does Willoughby, that only about half the variance of intelligence is due to genetical causes.

#### REGRESSIONS

Data which are unsuitable for correlation calculations can sometimes be used for determining regressions. For example, Burt (1943) has published figures comparing the mean mental ratios of fathers in different occupational groups with the mean ratios of their children. He showed that the children's mean

levels were always situated between those of the fathers and the mean IQ for the general population, 100. For example, fathers in the highly skilled clerical occupations had a mean IQ of 117.1 and the children of fathers in this class had a mean IQ of 109.1. Conversely, unskilled labourers were shown to have a mean IQ of 86.8 and their children's mean IQ was 92.0. If the means for children (or sons) of sets of propositi regress exactly halfway towards the general population mean, this would imply correlation coefficients of 0.5.

In the case of mothers, less information is available than for fathers. Occupational grouping has not been much used for estimating adult female intelligence in the normal range. However, the children of mentally defective parents have been studied and rated on many occasions, most defective parents were female. The enquiry, initiated by the Departmental Committee on Sterilization (1934), on defective parents produced figures showing that 16.9 per cent of the children were defective and 23.5 per cent were retarded. In four fifths of the cases the mother was defective, but test results were not published. Visser (1936) investigated the offspring of parents who had attended special schools and came to the conclusion that only very few of the new generation could be rated defective. The position is more easily understood when actual test results are given, as in the small but careful survey of Ainsworth, Wagner and Strauss (1945). The mean IQ of the defective mothers was 66.1 and that of the children 91.1 in 15 cases. This, like the results of similar enquiries (Brandon, 1957), indicates that the children of defective parents regress further towards the normal than would be expected if mental defect were due to additive genes alone.

Regressions for estimating the mental likenesses of sons, half-sons and cousins, can be obtained by testing relatives of defective propositi. If the investigation is confined to the fertile group, that is, to those patients with mental ratios above 50, fairly good approximation to the halfway regression points are obtained for sons. For half-sons or nephews and nieces, with additive gene inheritance of intelligence, we should expect regressions three-quarters of the way towards the normal average, and for first cousins, seven eighths. The observed and expected means, in a sample of tested propositi and relatives



taken from data of Penrose (1939a), are shown in Table XXIX. The patients in the fertile range, with I.Q. 50 or above, have sibs whose mean I.Q. is situated not far from the mid-point between their own mean level and 100. Half-sibs, nephews and nieces of a similar set of patients were found to have a mean I.Q.

TABLE XXIX  
MEAN STANFORD-BINET I Q FOR DEFECTIVE PATIENTS AND THEIR RELATIVES

	Type of Relationship to Patient	Number of Pairs	Patients' Mean I Q	Relatives' Mean I Q	
				Observed	Expected on Additive Gene Hypothesis
(i) Patients with I Q 50 or above	Sib	101	65.8	84.9	82.9
	Half-sib, nephew or niece	143	63.2	89.5	91.8
(ii) Patients with I Q below 50	Sib	120	24.2	87.4	61.1
	Half-sib, nephew or niece	90	33.3	95.1	83.3

situated not far from the point three-quarters of the way between the mean level of these *propositi* and 100. The results are in fair agreement with the hypothesis that intelligence level is due to additive genetical factors. On the other hand, for *propositi* with I.Q. below 50, the relatives of the same types are of considerably higher level than would have been expected on the same additive gene hypothesis. The mean I.Q. for these relatives of low-grade cases is still definitely subnormal, but genetical factors responsible for such low-grade defect cannot all be perfectly additive. In some cases the causal genes are completely or incompletely recessive. In others, new mutations or environmental accidents are responsible. A survey of the sibs of defectives, reported by Roberts (1952), confirmed the view that, among the *feeble-minded*, the genetical forces influencing intelligence level are multifactorial and additive, whereas, among the low-grade cases, other causes are more prominent.

#### THREAT OF DECLINE IN INTELLIGENCE LEVEL

The hypothesis that intelligence level is largely due to additive

community could therefore be an inverse consequence of the mean size of the family irrespective of genic background

Efforts have been made to answer by direct measurement the question as to what will happen to intelligence level in a community where children with low IQ have more brothers and sisters than children with high IQ. Along with other evidence of negative association between fertility and intelligence, this idea has motivated several enquiries comparing mean IQ of children at the present time with that of other children, tested in the same place in former years. A very substantial investigation was carried out by the Scottish Council for Research in Education (1949), the results of which can be summarized thus. In 1932, 87,498 children were given an intelligence test and their mean score was 34.5 points with a standard deviation of 15.5 points, in 1947, children of the same age groups as before, numbering 70,805, had a mean score of 36.7 with a standard deviation of 16.1. Over 1000 children, sampled at random, were given the Binet test in the two surveys and here there was no appreciable change in the mean. Family size had a correlation with intelligence measurement of  $-0.28$ , and, consequently, it is generally believed that the observed constancy of mental level, or even improvement, is a temporary effect due to environmental factors. Behind this facade, a decline is said to be in progress. Cattell (1950) and Emmett (1950) carried out surveys of comparable nature in other areas and were also unable to detect any deterioration.

#### EQUILIBRIUM OF INTELLIGENCE AND FERTILITY

Differential birth rate with respect to intelligence level is probably not a new phenomenon. It may have prevailed for a very long time. Bacon (1625), in his essay "Of parents and children", pointed out that "the Noblest workes, and Foundations have proceeded from Childlesse Men". In 1750, Short observed that "the most Laborious Part of Mankind are also the most fruitful in proportion to their numbers, and the most voluptuous, idle, effeminate and luxurious are barrenest, hard labour makes the Poor more fruitful". Galton (1869) drew attention to the surprising number of the ablest men who had left no descendants, as shown by historical records. If intelligence had been declining for many centuries or even for one

century, a decrease in the proportion of intelligent people in many countries would surely have been quite noticeable by now. The possibility that such differential fertility is a natural biological process, consistent with stable genetical equilibrium (Gorer, 1947), has rarely been considered. Could not the apparently greater fecundity in groups with relatively lower intellectual capacity be part of a biological compensatory mechanism? The key to such a process was actually known to Galton for he stated that, as giants and dwarfs are rarely prolific, so men of prodigiously large or small intellectual powers might be deficient in fertility.

It has been pointed out already that lethal recessive genes are lost when the homozygous type occurs in the offspring of carriers. The population can be in stable equilibrium, (i) if there are continual new mutations or, (ii), if the gene, in heterozygous form, confers a slightly increased fertility on the carrier. Exceptional vigour in heterozygotes is a phenomenon especially well known in plant genetics and is called heterosis (Gowen, 1952). Experimental evidence on *Drosophila* shows that the "carriers" of lethal recessive traits can often be fitter than the rest of the normal population. Moreover Barnett (1961) found that hybrid mice were more fertile and more adaptable to temperature changes than inbred strains. In a somewhat analogous manner, the almost normal carriers of genes that occasionally cause severe defects can be rather more fertile than the average. The increased fertility of mild cases can compensate for loss of genes in the relatively infertile severe cases. Eugenists are accustomed to draw attention to populations in which defects of all kinds are concentrated, which interbreed only among themselves and which are alarmingly fertile. This increased fertility, however, may represent a natural consequence of the prevalence, in the parents of heterozygous genes for lethal or sublethal defects.

Consider, for example, a purely hypothetical population divided into three groups. There will be a large group with slightly superior intelligence, say I.Q. 103, comprising some 90 per cent of the fertile population, and a small group with greatly inferior intelligence, say I.Q. 73, comprising 10 per cent, a "submerged tenth" or social problem group. Let us suppose that there is also a small infertile group of mental or physical

weaklings. We will assume that intelligence is due to a single perfectly additive pair of allelic genes,  $A$  and  $a$  that those in the upper group are all  $AA$ , that those in the small inferior group are all  $Aa$ , and that the weaklings are all  $aa$ . Further, let us assume, for the sake of simplicity, that mating takes place within the groups but never between them. There will be two types of mating only. In the slightly superior group,  $AA \times AA$  will produce nothing but slightly superior offspring  $AA$ . In the inferior group, the matings  $Aa \times Aa$  will give rise to  $\frac{1}{4}AA$  (superior),  $\frac{1}{2}Aa$  (inferior) and  $\frac{1}{4}aa$  (sublethal weaklings or imbeciles), who, we will suppose, do not survive or at least are not able to be parents. The perfectly additive nature of the gene will imply that these sublethal weaklings have an I Q of 43. When there is a tendency towards recessivity, the I Q of weaklings will be still lower. Now, this total population can be in perfect equilibrium with respect to the character, intelligence, if the birth rate in the inferior group is more than twice that in the superior group, i.e. 4.0 children as compared with 1.9 (see Table XXX). This is necessary because in the inferior

TABLE XXX

IMAGINARY POPULATION WITH COMPLETELY ASSORTATIVE MATING. INTELLIGENCE LEVEL DETERMINED BY A PERFECTLY ADDITIVE GENE PAIR

Types of Mating	Frequency of Mating Pair	Relative Birth Rate per Family	Offspring		
			$AA$ (I Q 103) Superior	$Aa$ (I Q 73) Inferior	$aa$ (I Q 43) Sublethal
$AA \times AA$	90	1.89	170	—	—
$Aa \times Aa$	10	4.00	10	20	10
All types	100	2.10	180	20	10
Parental pairs in next generation			90	10	—

group only half the offspring will replace the parental type. One quarter will contribute to the superior group and one quarter will be infertile.

Unless they possessed a greatly increased birth rate, the inferior group would gradually die out. In Table XXX there is exact replacement every generation. Note that the mean I Q

of the offspring is the same as that of the parents. It is also interesting to consider the fact that the birth rate of the inferior group would not need to be so high if mating were not so assortative, that is if the groups intermarried more at random.

It seems not unreasonable to suppose that both tendencies with respect to intelligence, assortative mating and differential birth rate, may be natural phenomena of long standing and part of a biological equilibrium, which has been established in past ages by natural selection. The hypothetical population, demonstrated in Table XXX, is very crude but it has a fair degree of resemblance to the conditions, believed by many observers to exist, in human communities. Burt (1946) stated that the children from the poorest social classes are greatly below the average in mental ability and have nearly double the average birth rate. Though poor economically and scholastically retarded, members of such groups may be biologically more fit than their apparently more favoured neighbours. The groups more lavishly equipped with genes for intellectual qualities not only depend upon the less scholastically inclined for manual labour but for replenishment of genic material. For replacement of intelligence genes lost on account of the relatively low fertility of the highly intelligent, the large birth rate of the supposedly inferior group is a necessity. This equilibrium is stable, that is to say, after a disturbance, the gene frequency tends to return to its former value. It is not interfered with by the occurrence in the population of extra cases of defect, evenly distributed among the offspring of superior and inferior groups, caused by other genetical processes or by environmental accidents. More realistic hypotheses, using an indefinite number of gene loci with additive effects which are in stable equilibrium, have also been investigated (Penrose, 1955).

## CHAPTER VII

### RARE AUTOSOMAL GENE DEFECTS

*Introduction—General Features of Dominant Traits—Huntington's Chorea—Dystrophia Myotonica—Epiloia—Neurofibromatosis—Acrocephaly—Miscellaneous Dominant Abnormalities—General Features of Recessive Traits—Description of Phenylketonuria—Genetics of Phenylketonuria—Other Specific Aminoacidurias—Hepatolenticular Degeneration—Galactosaemia—Cretinism—Retinitis Pigmentosa and the Laurence Moon Bardet Biedl Syndrome—Antiautistic Idiocy—Gargoylism and Related Diseases—Cerebral Diplegia—Friedreich's Ataxia—Microcephaly—Miscellaneous Recessive Abnormalities*

#### INTRODUCTION

THE account of hereditary diseases presented in this chapter is concerned mainly with autosomal conditions which are closely associated with mental subnormality. Some diseases, however, are discussed, which are only rarely found in connection with mental deficiency, because they clearly illustrate genetical processes less easily demonstrable in strictly relevant conditions. Dominant traits are described first and afterwards the much more extensive class of recessive defects. It will be observed that all the diseases concerned are rare. This is a necessary biological consequence of their severity which exposes them to the action of natural selection. This force tends to eliminate dominant diseases from the population efficiently but it has far less influence upon recessive defects. The result is that dominant traits connected with mental deficiency are fewer in number and less regular in manifestation than corresponding recessive traits.

#### GENERAL FEATURES OF DOMINANT TRAITS

*In human genetics a dominant defect is an abnormality which depends upon the presence of a gene in heterozygous form. Dominance is recognized in pedigrees mainly by continued transmission from parent to child. It follows that such a*

phenomenon can be observed only if an affected person is fertile. Thus, any easily recognizable dominant defect must be mild enough not to interfere seriously with reproduction. This comparative innocence of dominant defects is exemplified when there is constant manifestation of mild symptoms, as in night blindness, or when onset is postponed until after the reproductive period, as in glaucoma. Alternatively, the condition may have a variety of manifestations, so that some affected individuals are fertile whereas others are not. Variability may be expressed either in terms of severity of symptoms or in time of onset.

Any dominant disease severe enough to cause marked mental defect will also reduce fertility. Hence the gene responsible for such a trait must be variable in manifestation if dominant inheritance is to be recognized. Large degrees of variation in symptomatology and age of onset are, in fact, quite typical of the dominant diseases which are associated with mental defect. The result is that it is often difficult to establish the mode of inheritance, and exact Mendelian ratios are rarely exhibited.

When a gene causes dominant idiocy, the parent certainly cannot be similarly affected. Either he may show comparatively mild indications or complete suppression of the same disease. A third possibility is that the disease arises by new mutation in a parental germ cell and it first appears in a severely affected offspring who will be unable to transmit it. The occurrence of a defect, otherwise known to be dominant, in a single offspring of normal parents, with unaffected sibs, ancestors and collaterals, suggests this type of causation. If it were not for the recurrence of fresh mutation the genes responsible for dominant defects would quickly die out.

#### HUNTINGTON'S CHOREA

The most typical of rare dominant conditions associated with pronounced mental changes is the hereditary chorea first described by the American physicians, Waters, Lyon and Huntington, between the years 1841 and 1872. This disease is not characteristically a cause of mental deficiency but it illustrates certain principles of the genetics of dominant traits and it is worthy of mention at the outset.

Usually the disease begins in middle life with the gradual development of disorderly involuntary movements. As the choreic symptoms progress there is, commonly, a change in the mental state, producing eventually complete dementia. According to Bell (1934), about one third of the cases remain free from mental symptoms. The age of onset varies from 5 to 70 years and is slightly earlier in females than in males. The mean, given by Bell for 460 cases of both sexes, is 35.5 years, with a standard deviation of 12.4 years. Only if dementia occurs before or during adolescence can it be classified reasonably as mental defect.

The cerebral pathology is a chronic degeneration not only of the nerve elements in the cortex but also of those in the thalamus and corpus striatum. The biochemistry of the changes is at present unknown. The progressive nature of the lesions should make fairly easy the differentiation of these patients from those with other types of disease, affecting the corpus striatum, causing choreic or athetoid involuntary movements.

Biologically there are several points of interest. The illness arises relatively late in life, so that it does not seriously interfere with the fertility of most of those whom it affects and it can be clearly seen to have dominant inheritance. There is, moreover, a significant relationship between the ages of onset in affected members of the same family. According to Bell (1942), the correlation of onset age in parent and child is 0.59 and between sibs it is 0.46. These figures indicate that the age of onset variations are determined genetically and depend upon factors at loci unrelated to that at which the main causal gene is situated. When the disease appears in a family where previous generations were unaffected, it may be supposed to have arisen by new mutation in a germ cell of a normal parent. According to Reed and Neel (1959) the estimated rate of mutation of normal genes to abnormal alleles, which produce Huntington's chorea, is 5 per million per generation.

#### DYSTROPHIA MYOTONICA

In the next clinical group which comes into consideration there appear to be three distinct diseases, they have sometimes been classed under the generic name of myotonia (Bell 1947). The earliest to be recognized was a clearly dominant condition,





Plate I—Epiloia in a male epileptic imbecile aged 28  
Note the typical sebaceous adenomata around nose and mouth and  
the raised plaque on forehead

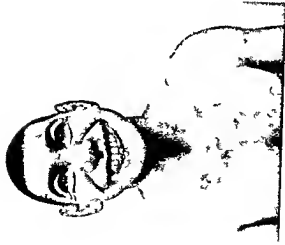


Plates IIa and IIb—Phenylketonuric patients brother aged 16 with I Q 40 and sister aged 20 with I Q 20 (Munro 1947 Fam ly No 3) The hair of these patients was darker than s usual in phenylketonur a Note the mannerist c position of the sister s hands



Plates IIIa and IIIb—Laurence-Moon-Bardet-Biedl syndrome in a feeble-minded male aged 30 He has retinitis pigmentosa, obesity and polydactyly on the right foot The parents were first cousins once removed Three sisters were normal and one sib, who died in infancy, had six toes on one foot once removed





Plates IVa and IVb—Recessive Microcephaly in a male idiot aged 32 Note the small cranium with dysplastic ears and the well developed shoulders Head measurements breadth 117 mm length 154 mm height 106 mm cephalic index 0 76 The pedigrice is shown in Figure 7 (i)



a



b

Plate Va and Vb—Sex linked gargoylism male aged 13 (Millman and Whittick 1952)

Note dwarfed stature, short neck and relatively large head, facial dysplasia, deformed joints and protruding abdomen



Plates VIa and VIb—Naevoid amentia Sturge Weber-Kalischer syndrome Female epileptic imbecile, aged 12 On the right side she has both parietal naevus and calcified cerebral vessels seen in the X ray There is nemioplegia on the left side of the body



*Plate VII—Mongolism in two imbecile brothers aged 10 (Colchester Survey, 1938, Case No 740) and 5 years with a normal child aged 2½ years*

As compared with the normal child, the younger mongoloid is seen to have a small head, decreased stature and dysplastic features

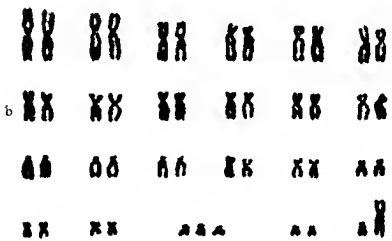


Plate VIII—Mitotic cell with analysis from dermal culture (the older patient shown in Plate VII) The karyotype is standard male mongol trisomic for No 21



myotonia congenita, or Thomsen's disease, in which the chief symptom is inability to relax muscles of the limbs immediately after their contraction. Mental deterioration does not accompany the disease, but psychosis may develop in later life. The second disease in the group, known as paramyotonia, is a rare intermittent type of Thomsen's disease in which the symptoms are precipitated at any age by exposure to cold.

A more common disease, but still very rare, also inherited as a dominant trait is dystrophia myotonica. The incidence is about one in 50 000 in the general population (Lynas, 1957). The clinical picture is variable, but the syndrome is nevertheless quite characteristic. In the most severe cases, mental defect is associated with myotonic symptoms, muscular wasting, frontal baldness and cataract. Subjects are usually normal at birth and the disease is slowly progressive. Myotonia, shown by stiffness of movements of the hands and feet, commonly appears in early adult life with wasting of the affected muscles, especially in the forearms and the sterno mastoids, tendon reflexes are diminished. The cataract is of a peculiar type, beginning at about the age of 30 with small peripheral opacities detectable only with a slit lamp.

The age of onset of dystrophia myotonica is variable, the mean is 24 years, with a standard deviation of 13 years, and the pathological changes which take place are related to the time of onset. Mental defect is an accompanying symptom only when the onset is early. If mental deterioration takes place in later life, dementia would be the correct designation. The few cases of dystrophia myotonica admitted to hospitals for the mentally defective are likely to be in the feeble minded class though some recorded pedigrees contain cases of severe defect present from birth.

Dystrophia myotonica is remarkable in that affected sibs have similar symptoms and onset ages, whereas affected parents and their affected children can have very different ages of onset. Transmission is sometimes through individuals who are apparently quite normal. A satisfactory explanation of this mode of inheritance, which was first considered by Goldschmidt (1938), is that it results from interaction between alleles at the gene locus in question. The same kind of allelic modification has been studied by Renwick (1956) in the nail patella syn-

drome and it has been found in some other dominant traits

The lack of correlation for onset age in parent and child allows the phenomenon of anticipation to be very noticeable. Some authorities still hold the view that when a mild form of the disease (e.g. cataract only) occurs in the parent and a severer form (e.g. dystrophy and mental defect) occurs in the offspring, this indicates a real process of worsening in succeeding generations. However, when the effect of selecting families by severe disease in the offspring has been fully examined, this hypothesis is seen to be unnecessary (Penrose, 1948). The effect is enhanced by the biological fact that severe cases in which the disease is of early onset, are unlikely to appear among the parents (Chapter IV pp. 74-8).

#### EPILOIA

The syndrome of tuberose sclerosis, sebaceous adenoma and epilepsy produces a highly characteristic problem in the genetics of mental defect. The condition was first recognized by Bourneville (1880) and the name epiloia was suggested by Sberlock (1911) to indicate the whole variable pathological complex. Most noticeable is the 'butterfly' rash on the cheeks, nose, chin and forehead, sometimes mistaken for an inflammatory eruption such as acne rosacea. The rash is due to tumours fibrous in consistency and considered to be sebaceous adenomata, which begin in early childhood and develop slowly. Those on the face reddish and vascular, were first fully described by Pringle (1890). Similar tumours, or plateaux of hard skin, occur on other parts of the body, notably on the scalp and the back, and these are usually brownish or white in colour. The nail beds are sometimes involved. The distributions of skin lesions tend to be roughly, though not precisely, symmetrical. Pigmented naevi and soft neurofibromata have occasionally been described in these cases also. The condition is illustrated in Plate I.

Associated with the skin lesions is a condition known as tuberose sclerosis of the brain. Multiple nodules are found in the cortex and other parts of the brain substance. They may occur in the ependyma of the lateral ventricles and in the cerebellum. The consistency of these tumours has been likened to cartilage, rubber or potato (hence the name tuberose), and

in the ventricles they have the appearance of candle gutterings. Histologically they are shown to be mainly gliomata containing large multi-nucleated cells and undifferentiated nerve elements (Bielschowsky and Gallus, 1913). Paralysis with signs of pyramidal lesions does not occur as commonly as the gross cerebral pathology might suggest. Other rare types of tumour are found in different parts of the body in this disease. These include (i) striated muscle tumour (rhabdomyoma) of the heart, (ii) a mixed kidney tumour also containing striated muscle cells and (iii) nerve tumours of the retina (benign phakomata) which appear as grey plaques under ophthalmoscopic examination. Abnormalities of the bones, patches of periosteal thickening and rarefaction have been described (Gottlieb and Lavine, 1935). Lung cysts may develop and cause respiratory symptoms (Dawson, 1954).

The mental symptoms of the condition vary from profound idiocy to psychosis. Epilepsy is almost always present in severe cases. There may be long intervals between fits but sometimes they are of extremely frequent occurrence. On the other hand, sebaceous adenoma can occur without being associated with any obvious mental disturbance at all. Also, epilepsy may be the only symptom in the absence of mental defect or visible skin tumours. The disease shows a perplexing variety of manifestations in different patients, and cases with almost every combination of signs have been found. This is shown by Farber's (1931) autopsy records of 27 cases of rhabdomyoma of the heart, in which he found tuberosc sclerosis associated in 18 cases, kidney tumours in 14 cases and sebaceous adenoma in at least four. The presence of two or more of these rare conditions in the same individual can hardly be attributed to chance. It is probable that the whole group of lesions and the mental disturbances are pleiotropic effects of a single abnormal gene which is irregularly dominant. In consequence of great variability of manifestation, precise Mendelian ratios are not likely to be found in sibships.

The interpretation of family histories in cases of epiloia is made especially difficult because, even in the same family, the affected persons may show quite different signs. Fuhs (1925) traced the condition through five generations. This, however, is exceptional. In most published pedigrees only two or, at most,

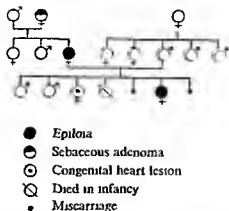


Figure 7—Pedigree of *epiloia* (Gunther and Penrose 1935, Case No 8)

three generations have affected members. Figure 7 shows a pedigree where the disease occurred in grandmother, mother and in at least one of her daughters. In about half the severe cases associated with mental defect, and perhaps in more, it is impossible to trace any indication of familial incidence. Cockayne (1933) pointed out that, though there was clearly a tendency to dominance in certain families, in others new mutation may be held responsible. In some families, though the parent may not show the disease, he may carry the gene.

One or two families have been reported in which recessive inheritance would naturally be postulated because parents were both normal and consanguineous. Consanguinity can occur occasionally in the parents of individuals with dominant abnormalities, as in the general population. Although the possibility that a recessive type exists cannot be excluded, this seems unlikely in view of the findings in Borberg's (1951) survey, i.e. no parental consanguinity in 37 families. Neglecting this consideration, the frequency of *epiloia* due to a dominant gene in the general population in England can be estimated at one in 30,000. If half the cases were the result of new mutations, an estimation of the mutation rate can be made. Since each individual carries two loci at which mutation might occur, this would amount to  $1/2 \times 1/30,000 \times 1/2$ , that is one in 120,000, or 8 per million, gene locus per generation (Gunther and

Penrose, 1935) From this result it seemed that, taking the generation time as a unit, man may be somewhat more mutable than *Drosophila*

Analysis of known family histories shows that there is a tendency for the severity of the disease to be greater in some families than in others Sometimes only sebaceous adenoma is found in several members as the main symptom (Shelmire, 1918), in others a more complete syndrome may be repeated Berg (1913), for example, observed a father and daughter both with sebaceous adenoma, tuberosc sclerosis and kidney tumours, though the father's father had a kidney tumour without other features More usually affected members in the same family show great variety in the signs and symptoms they possess As in Huntington's chorea, the cause of these variations can be most credibly attributed to independent modifying factors (Marshall, Saul and Sachs, 1959) Environment has not been shown to play any significant part in the aetiology The sexes are equally affected On the average, fathers' and mothers' ages are probably somewhat greater than in the general population Order of birth is without demonstrable influence

The grade of defect in hospital cases of epiloia may be very low (see Appendix 8) and a certain amount of slow deterioration occurs The rare phenomenon of a dominant gene which is responsible for a very severe type of defect is made possible both by the variable manifestation of the causal gene and its recurrent mutation

#### NEUROFIBROMATOSIS

Multiple nerve tumours of the type described first by von Recklinghausen (1882) are sometimes found associated with mental deficiency Characteristic tumours are mostly small and subcutaneous They enlarge progressively and sometimes occur in enormous numbers, covering the whole body, patches of pigmented skin are usually present Hashimoto (1890) counted 4,503 tumours on the skin of a middle aged Japanese man suffering from the disease

Neurofibromatosis is sometimes associated with a mild degree of subthyroidism Affected persons are usually short of stature Preiser and Davenport (1918) found that nearly 10 per cent of the cases are definitely mentally defective

Numerous family histories have been collected (Cockayne, 1933) and they are, on the whole, consistent with the hypothesis that an irregularly dominant gene is responsible. The general appearance of the findings in pedigree studies (see Figure 8) is

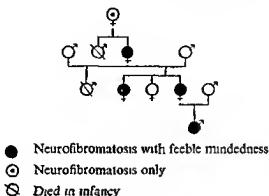


Figure 8 —Pedigree of neurofibromatosis (Colchester Survey 1938, Case No. 255)

not unlike that shown by epiloia. Some cases appear to be due to new mutation. In both diseases latent forms may occur. There are some common factors also in the cerebral histopathology, for example the occurrence of giant cells. However, the diseases are quite distinct clinically. No obvious relationship holds between the severity of neurofibromatosis and the degree of mental impairment. Furthermore, defectives with neurofibromatosis are seldom found among the low-grade cases (see Appendix 8). The incidence of all types of the disease, including those in which the only sign is pigmented skin patches, is greater than one in 2000 of the general population (Neel, 1954).

#### ACROCEPHALY

Among the curiosities of head shape found among the mentally defective is a type known as acrocephaly or oxycephaly. This means that the head is high or pointed, in metrical terms, the vertical measurement is abnormally great in comparison with length and breadth. The mean head measurements of adult male acrocephalic defectives, sorted out on clinical

grounds, are given in Table XXXI. The vertical measurement in acrocephaly is seen to be greater and the whole cranium wider and shorter than the average in a control group of adult male patients. It is doubtful whether there is a single type of acrocephaly or a number of different closely related types.

TABLE XXXI  
MEAN HEAD MEASUREMENTS (mm) IN GROUPS OF ADULT MALES

	Breadth (i)	Length (u)	Height (m)	Cephalic index (i)/(u)
5 Acrocephalics	153.4	180.8	136.6	0.85
10 Microcephalics	131.6	180.0	115.5	0.73
11 Mongols	142.5	174.6	125.7	0.82
All types of defectives of comparable grades	146.9	188.3	131.2	0.78
General hospital population (Goring 1913)	149.3	190.4	132.9	0.78
Australian control population (Berry and Porteus 1920)	152.5	193.7	134.6	0.78

In the classical craniofacial dysostosis, originally described in 1912 by Crouzon (1929), the skull deformity is associated with exophthalmos; bony pressure is believed to cause atrophy of the optic nerves but evidence for this view is meagre. The skull itself tends to be thin, especially at the vertex, and X-ray examination reveals irregularities of texture known as "digital" markings. These markings are due to local rarefaction of the bone and they do not correspond with the underlying convolutions. The Crouzon type of acrocephaly has been repeatedly traced in more than one generation of a pedigree. The inheritance appears to be dominant and the sexes are equally affected. The gene, like those responsible for other dominant defects, tends to have a variety of degrees of manifestation. If mental defect is present, it tends to be mild. Cases arise from time to time by fresh mutation, a credible explanation if a severe case arises in a family where no similar condition can be traced after careful search. Ferriman (1941) found that the majority of acrocephalic cases were, in this way, sporadic, but uncertainty that mutation is the cause of a given case always remains when, as here, dominance is irregular.

Acrocephalosyndactyly, originally described by Apert (1906),

is a crippling deformity in which the hands and feet are seriously malformed by a welding together of the ends of the digits and associated skull peculiarities are even more marked than in the Crouzon type. Mental defect, though again usually not of a severe degree, is a common accompaniment. Nearly all the cases are sporadic and can be assumed to be due to fresh mutations. Exceedingly rare examples of transmission from parent to child confirm the hypothesis of single gene dominant inheritance. Blank (1960) estimated the rate of mutation to the abnormal gene responsible for the condition to be 3 per million per gene locus per generation. Advancing age of the father was shown to be a predisposing factor.

A condition related to acrocephaly, though the head is too wide laterally rather than too high vertically, is known as hypertelorism and is characterized by abnormally increased distance between the eyes. Mental defect is usually associated when the deformity is severe. A fundamental anomaly in this as in the acrocephalic types, is premature synostosis of the components of the cranial base. In hypertelorism the sphenoid bone, in particular, is abnormally shaped and the sella turcica may be deformed to the detriment of development of the pituitary gland. The osseous peculiarities were described by Greig (1924). Affected individuals may show signs of obesity and hypothyroidism, which perhaps is secondary to dyspituitarism. It has been claimed that hypertelorism appears in families as a dominant character, in such cases it may be a variant of cranio facial dysostosis not necessarily connected with mental changes (Abernethy, 1927). The relationship between interpupillary distance, and clinical type of defect has been investigated by Kerwood. Lang Brown and Penrose (1954).

#### MISCELLANEOUS DOMINANT ABNORMALITIES

Some dominant skeletal defects are encountered, from time to time, among the mentally defective just because, by random assortment, two anomalies will occasionally coincide in the same person. It has sometimes been assumed if such a condition as the lobster claw deformity or other type of ectrodactyly occurs in a mentally defective subject, that the two are causally connected (Weygandt 1936). The lobster claw deformity and cleidocranial dysostosis are two dominant conditions with



variable manifestation in some pedigrees, but in neither of these malformations is mental defect a characteristic feature.

The position of achondroplasia, now usually called dyschondroplasia or chondrodystrophy, is similar. This is a very well known condition first properly distinguished by Parrot (1878). A disturbance of the growth of all cartilaginous bones leads to gross shortening of the limbs. The deformity appears to be due to a dominant trait with somewhat irregular manifestation, and it has been occasionally observed in association with mental defect (Morris and MacGillivray, 1953). Mørch (1941) studied a large series of cases from the genetical point of view. Transmission of the fully developed condition from parent to child is a rarity, and the majority of cases are thought to be due to fresh mutation. The incidence rises significantly with increasing age of the father.

In a condition which is, superficially, the converse of achondroplasia (Olcott, 1940), long spidery fingers and toes, combined with long limbs, are found together with coloboma, dislocation of the lens of the eye and congenital heart defect. The syndrome is named after Marfan (1896) who first drew attention to it. Sometimes there is also a narrow thorax with marked kyphosis and a long, narrow head. There are many pedigrees on record which indicate transmission of a single main gene from parent to child. Mental defect is not considered to be an essential feature, but numerous instances of its concurrence with arachnodactyly are known. Usually they appear in families as isolated cases and the signs and mental grades vary greatly from one patient to another (Dax, 1941). As in achondroplasia, most instances are attributed to fresh mutation (Lynas, 1958) and advancing paternal age seems to be aetiologicaly significant.

Another rare condition, *hyperostosis frontalis interna*, possibly transmitted as an irregular dominant (Knies and le Fever, 1941), is sometimes associated with mental defect. The disease is characterized by progressive thickening of the frontal region of the skull together with atrophy of the cerebrum. It occurs most noticeably in females and may be accompanied by endocrine disorders, such as obesity, attributable to disturbance of pituitary function or to disordered metabolism. As the onset of the condition is usually in adult life, the loss of mental

power which follows is usually diagnosed as insanity and not defect. The brain atrophy may be an essential part of the disease and not just a secondary effect of the bone changes, but Stewart (1941) has shown that the cerebral atrophy is not the cause of new bone formation, as some had thought.

An extremely rare developmental abnormality of the brain, characterized chiefly by absence of the olfactory nerve tracts and known as arhinencephaly, has been observed in idiots (Stewart, 1939). There are associated defects of the nose, maxilla and palate in the mid line as well as hypoplasia of the cerebral hemispheres. The condition has been observed by Grebe (1944) in several members of the same family. Two affected brothers had two paternal uncles and one other paternal relative similarly affected. Surviving cases were feeble-minded and each showed median cleft palate, hypoplasia of nasal septum and absence of olfactory sense. Other relatives may have been very slightly affected. A heterozygous gene with irregular manifestation is possibly the basic cause of arhinencephaly.

Aniridia (congenital absence of the iris) has been reported in families as a fairly regular dominant character. The majority of cases are sporadic and these may be the result of new mutation. Møllenbach (1947) considers that the malformation is

TABLE XXXII

INCIDENCE AND GENE MUTATION RATE IN SOME RARE AUTOSOMAL  
DOMINANT DEFECTS

Condition	Approximate Incidence per million in general population	Estimated Mutation Rate per million gene loci per generation	Source
Huntington's chorea	40	5	Reed and Neel (1959)
Dystrophia myotonica	20	8	Lynas (1957)
Epiloia	33	8	Gunther and Penrose (1935)
Acrocephalosyndactyly	6	3	Blank (1960)
Achondroplasia	105	45	Merch (1941)
Arachnodactyly	15	6	Lynas (1958)
Aniridia	11	5	Møllenbach (1947)

*The mutation rate per individual, which is twice the rate per gene locus, is about the same as the incidence of severely affected non-fertile cases in the general population*

significantly associated with diminished intellectual capacity. He has estimated that the mutation frequency is about 5 per million per gene locus per generation. Not all the cases, however, are necessarily of the same genetical type. Schachter and Ourgaud (1948) made observations on the association of aniridia and mental defect in two pedigrees. A comparison of mutation rates estimated for gene loci, responsible for several dominant diseases, is shown in Table XXXII.

#### GENERAL FEATURES OF RECESSIVE TRAITS

Recessive defects depend upon the presence of two precisely similar genes, one derived from each parent. In rare diseases with this type of causation, the homozygous recessive defective has normal parents, who are both heterozygous for the gene in question.

Rare recessively determined defects are usually more severe and their manifestations vary less from patient to patient than dominant abnormalities. Family histories are highly characteristic. Sharp segregation between affected and unaffected sibs is the rule and parental consanguinity is a most useful sign. In diseases which are associated with mortality early in life, evidence of inbreeding carries more weight in the diagnosis of a recessive defect than the estimation of Mendelian ratios.

Natural selection acts against recessive defects very slowly because the heterozygous carrier need not be abnormal in any way although the homozygote may be quite infertile or even non-viable. In some diseases, however, the carriers may show mild or abortive signs of the recessive trait and these signs are inherited as irregular dominant characters. A summary of known instances of such tendencies towards intermediate inheritance was made by Neel (1947). Since then, many new examples have been described. A common method of detecting heterozygotes is by using a tolerance test, as in phenylketonuria and galactosaemia.

If heterozygous carriers are endowed with even a minute advantage in fertility as compared with the rest of the population, genetical equilibrium can be maintained in spite of the elimination of occasional infertile homozygotes. This fact makes the mutation rate of genes causing recessive defects very difficult

to estimate even in a population where the degree of inbreeding is constant

Recessive mental defects, found mainly among the idiots and imbeciles, are rare. They have frequencies of the order of 1/50 000. Biologically, their importance lies partly in the fact that most people in the general population are heterozygous carriers of one or more recessive genes capable of producing severe abnormality in the offspring, if mating occurred between two people carrying similar genes. The presence of such genes may be unsuspected until inbreeding takes place. By experimental inbreeding in cattle, Mead, Gregory and Regan (1946) discovered six or seven recessive abnormalities among the progeny of six dairy bulls of supposedly good stock. In human populations, the parallel method is to examine the progeny of consanguineous parents and compare them with those of unrelated parents, on the assumption that the offspring of cousin parents will contain examples of rare recessive abnormalities. For example, the familial incidence of defect, especially low-grade defect, is found to be significantly greater in sibships for which parental consanguinity is present than in those for which it is absent. As can be seen in Table XXXIII, the incidence of stillbirths, and that of deaths in early infancy, is also

TABLE XXXIII

MENTAL DEFECTS IN SIBS OF PATIENTS WITH AND WITHOUT RELATED PARENTS Colchester Survey 1938

		Parental Consanguinity	
		Present	Absent
Number of patients		45	1235
Number of sibs		254	6375
Percentage of sibs			
Normal intelligence	Superior	0 8	1 0
	Average	47 2	55 3
	Dull	9 1	7 4
	Unascertained	3 1	3 4
Mentally defective	Feeble-minded	4 3	4 1
	Imbecile	2 8	1 7
	Idiot	3 1	0 7
	Miscarriage or stillbirth	15 4	13 6
Died in early infancy		14 2	12 8
Total		100 0	100 0

increased slightly in the consanguinity group. A correlation between stillbirth rate and cousin marriage in different districts of France was observed by Sutter and Tabah (1952). Comparisons between the offspring of consanguineous and control marriages from the general population have been used for estimating the prevalence of all types of recessive traits. Much relevant material has been summarized by Stern (1960). It is deduced that, on the average, every person is a heterozygous carrier of about two rare genes which, in the homozygous state, cause mortality in early life.

#### DESCRIPTION OF PHENYLKETONURIA

A Norwegian biochemist, Folling (1934), first described an abnormality of which an essential feature was the urinary excretion of about 1 g daily of phenylpyruvic acid, a ketonic acid with the formula,  $C_6H_5CH_2COCOOH$ . The excretion is first observable in early infancy and is usually continuous throughout life. Occasional cases showing intermittent excretion have been recorded. Nearly every case shows intellectual defect, commonly of a severe degree.

The name "phenylketonuria" (Penrose and Quastel, 1937) seems preferable to the original, more cumbersome designation "imbecillitas phenylpyruvica" and also to "phenylpyruvic oligophrenia", favoured by some American workers. The shorter name emphasizes the biochemical nature of the abnormality and brings the nomenclature into line with that of other comparable abnormalities, such as alkaptonuria, cystinuria and pentosuria.

The test for phenylpyruvic acid in the urine is simple and striking. When the acid is present, a deep bluish green colour, which fades within a few minutes, is obtained on the addition of a few drops of 5 per cent ferric chloride solution. If desired, alkaline urines can first be neutralized by the addition of dilute sulphuric acid. The urine has also a detectable aromatic odour. "Phenistix", an impregnated strip, like litmus paper, which is dipped into urine, provides a convenient alternative test (Gibbs and Woolf, 1959). A positive reaction is indicated by a green colour. The test can be done on an infant's napkin.

The clinical picture is peculiar in many ways. To the casual glance these patients appear to be just ordinary imbeciles, but

the skilled observer may occasionally diagnose a case correctly before the urine has been tested. Some 60 per cent of the cases are of the idiot grade and 30 per cent imbecile. The grades of the remaining 10 per cent range from mild subnormality to average. There is a tendency for the same grade to be repeated in different affected members of the same sibship. Most patients are good tempered and those with sense enough to learn to talk are cooperative and friendly. Hyperkinesis, which takes the form of digital mannerisms, is often conspicuous in low-grade cases. Some of the patients have epileptiform seizures in infancy and childhood. Phenylketonuria has been ascertained more frequently in females than in males, but this difference may arise simply because females are healthier and live longer than the males. Two cases are shown in Plates IIa and IIb.

Among the distinctive physical features in severe cases are dwarfing of stature and reduced head measurements as compared with the normal average. The incisor teeth tend to be widely spaced and the skin, which may show variable pigmentation, is unduly subject to dermatitis. There is sometimes a tendency to excessive sweating. Kyphosis is very common. On the neurological side, the constant feature is accentuation of all reflexes, both superficial and deep, in a manner reminiscent of the brisk responses obtained in hyperthyroidism. Ordinarily there is no paralysis and no increase in muscular tone, though Jervis (1937) asserted that spasticity is a typical finding. Fair hair and blue eyes (Berg and Stern, 1958) are very common characteristics. In some Norwegian patients the hair was almost colourless, as in the albino. Comparison of hair colours of the imbeciles with those of their normal brothers and sisters indicates that dilution of hair pigment is part of the syndrome (Cowie and Penrose, 1950), though, as with normals, the shade darkens with maturity.

On the whole, the physical health of these patients is surprisingly good. No very characteristic pathological changes have been observed at autopsy. The ferric chloride test for phenylpyruvic acid made on all tissues gives negative results. Degenerative changes in the cortex, basal ganglia and in the liver were described by Delay, Pichot, Polonovski, Desgrez and Delbarre (1947). In one instance, multiple nerve tumours were found (Penrose, 1939b), but the association may have

been fortuitous. Summarizing reports on 24 examinations, Crome and Pare (1960) concluded that diminished brain size and fibrous gliosis of the white matter were the main abnormalities.

The pathological chemistry of phenylketonuria has raised two main questions (i) Where does the phenylpyruvic acid come from? (ii) How is the anomaly which allows this abnormal metabolite to be excreted related to the associated mental peculiarities? The first question has been fully answered but the second still remains open. The quantity of the acid excreted depends on the diet. It can be increased by feeding either laevo- or dextro-phenylalanine and abolished, temporarily, by a protein free diet or, more permanently, by a synthetic phenylalanine-free diet. Feeding with excess of amino acids other than phenylalanine, such as tyrosine and alanine, does not increase the quantity of phenylpyruvic acid in the urine. Thus phenylalanine, although a common and necessary constituent of ordinary diet, must be the source of the abnormal acid which is produced from it by deamination (Krebs, 1935). Phenylalanine itself also occurs in the urine together with other derivatives, phenyllactic, phenylacetylglutamic and *o*-hydroxyphenylacetic acids. Concentrations of laevo-phenylalanine thirty times as great as the normal are demonstrable in the blood and in the cerebrospinal fluid. Jervis (1947) showed fairly convincingly that the main error is inability to produce tyrosine from phenylalanine. Since then, by testing liver substance obtained at autopsy, Jervis (1953) demonstrated that an enzyme, normally present in that organ and capable of performing this change, is absent in phenylketonuria. Thus the fundamental defect is absence of a critical enzyme, phenylalanine-hydroxylase.

The relationship of the chemical anomaly to the mental subnormality in this disease is not understood. The brisk reflexes observed, which resemble those in thyrotoxicosis, suggest that *poisonous metabolites are present*. So also does the gradual mental deterioration which is often seen during the early years. Experiments on monkeys have shown that large doses of phenylalanine added to the diet retard growth and interfere with mental development (Waisman, Wang, Palmer and Harlow, 1962). Treatment of phenylketonuric patients by

diets low in phenylalanine does not seem to produce appreciable improvement of mental ability in children or in adults. It is, however, claimed that if such treatment can be started soon after birth and continued for years normal development is possible (Blainey and Squire, 1962). Since untreated patients have been described in whom phenylketonuria coexists with approximately normal intelligence (Woolf, Ounsted, Lee, Humphrey, Cheshire and Steed, 1961, Cowie and Brandon, 1958), the effects of dietetic experiments upon IQ level are difficult to evaluate. According to one view (Bessman and Tada 1960) the main toxic substances may be indole compounds produced by errors in tryptophane metabolism, perhaps a secondary result of phenylalanine oxidase failure. Himwich and Fazekas (1940) attributed the low level of mental activity in phenylketonurics to diminished rate of oxidation found in the cerebral circulation. Changes in pigmentation are not so difficult to explain as mental changes. Melanin defects could be caused by interference with tyrosine metabolism associated with the excess of phenylalanine. It is noteworthy that in an inherited condition in mice comparable with phenylketonuria dilution of pigmentation is an important feature (Coleman, 1960).

#### GENETICS OF PHENYLKETONURIA

Pedigrees of phenylketonuria can be interpreted without much hesitation as demonstrations of the mode of inheritance of a rare recessive Mendelian trait. The main features include significant familial incidence, which is practically always confined to brothers and sisters. Environmental agencies such as those which might be connected with maternal age and order of birth, do not appear to be of significance. There is sharp segregation between normal and abnormal members of the family. Cousin parents are relatively frequent. The recessive hypothesis has been further strengthened by calculating the probable magnitude of the ratio of affected to normal members in sibships. After making due adjustment for mode of ascertainment, the ratio is very close to one in four (see Table XXIV). In two exceptional families in the United States, cited by Jervis (1937), the mothers were phenylketonuric. Nearly always parents have been reported to be of average mental capacity. In the great



majority of instances they have been examined and proved not to be excretors of phenylpyruvic acid. In 47 families, analysed in Table XXIV, all the parents were unaffected and five pairs (10 per cent) of them were first cousins. Jervis found that 5 per cent of the parents of the phenylketonurics in United States hospitals were first cousins. Of the parents of Norwegian patients, 14 per cent were first cousins (Fölling, Mohr and Ruud, 1945) (Table XXXIV). All these percentages are significantly higher than the frequencies of first-cousin marriages in the general populations concerned, which are probably lower than 1 per cent and may be as low as 0.6 per cent.

TABLE XXXIV  
PHENYLKETONURIA IN FAMILIES

Source	Initial Cases	Brothers and Sisters		Parents		
	Phenylketonuric	Phenylketonuric	Normal	Phenylketonuric	Normal	First Cousins
Munro (1947)	47	38	141	0	94	10
Jervis (1939)	125	72	270	2	248	14
Fölling <i>et al</i> (1945)	22	18	86	0	44	6
Total	194	128	497	2	386	30

The frequency of phenylketonuria in the general population was estimated by Munro (1941) to be about one in 50,000 in the United Kingdom and by Jervis (1937) to be about one in 25,000 in the United States. In Norway the incidence may be a little greater. These incidence frequencies are likely to be approximately correct and they lead to agreement between expected and observed proportions of first cousin parents when the Lenz formula (Appendix 5) is applied. The high incidence in Norway may, however, be illusory because the distribution was found to be uneven. In one small region, Hvaler, a single ancestor possessing the gene might have been responsible for the four cases found there. The gene frequency, best calculated as in Table XXXV from the square root of the incidence of cases with unrelated parents, amounts to one in 173 in the United States and one in 245 in the United Kingdom. The frequency of

carriers of the gene, which is almost double the gene frequency, is thus of the order of one in 100.

TABLE XXXV  
GENE FREQUENCY OF PHENYLKETONURIA

Survey	Caste Frequency* ( $q^2$ )	Gene Frequency ( $q$ )	Carrier Frequency ( $2q(1-q)$ )
United States	1/30,000	1/173	1/86
United Kingdom	1/60,000	1/245	1/122

\* Excluding cases known to have consanguineous parents

Cases of German, Irish, Italian, Slavonic and Dutch origin have been found in the United States but the disease is exceedingly rare among coloured Americans. Judged by local surveys, the incidence is high in France (Rhem and Stoeber, 1936) and low in Switzerland (Brugger, 1942). In his survey of cases in the United Kingdom, Munro (1941) found a rather higher incidence in the west of England than in the east, particularly in the north-west. The distribution of the ABO blood antigens in phenylketonurics and their sibs showed a higher incidence of B than did the English population from which these cases were drawn. According to Carter and Woolf (1961) the phenylketonuria gene is much commoner in Ireland and in west Scotland than in England. A survey in Japan (Tanaka, Matsunaga, Handa, Murata and Takehara, 1961) showed that the incidence of the disease was about one in 60,000. In Ashkenazi Jewish populations, throughout the world, the condition is rare (Cohen, Bodonyi and Szemberg, 1961).

It is important to ascertain what effects, if any, are produced in heterozygotes by the phenylketonuria gene. No physical or mental abnormalities are specially prevalent among presumed carriers though there is some evidence that they may be predisposed to develop a depressive type of psychosis at the age of about 50 years (Munro, 1947, Thompson, 1957). Indirect measurement of phenylalanine-hydroxylase activity, by investigating both the fasting blood level of phenylalanine and the level after exposure to a large dose of the substance, is possible. In this way a minor defect of enzyme efficiency in carriers can

be detected Hsia, Driscoll, Troll and Knox (1956) compared the tolerance to doses of 0.1 gm laevo phenylalanine per kg body weight in parents of phenylketonuric patients and controls. Discrimination between the two groups is best obtained by testing the blood four hours after drinking the dose and it has 90 per cent efficiency (see Figure 9). The defects of indole meta-

Blood Phenyl-  
alanine mgm%

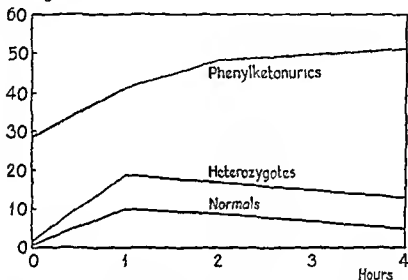


Figure 9 — Blood phenylalanine levels obtained in the course of tolerance tests (after Hsia 1957)

bolism, found in phenylketonurics by Pare, Sandler and Stacey (1957), have been investigated in carriers by Hsia, Rowley and Huang (1961), reduced urinary excretion of 5 hydroxyindoleacetic acid after phenylalanine loading was observed in heterozygotes as compared with controls. Detection of heterozygous carriers is of special significance in relation to problems of eugenic prognosis, it also has biological value in the search for genetical linkage (Renwick, Lawler and Cowie, 1960).

#### OTHER SPECIFIC AMINOACIDURIAS

The discovery of phenylketonuria and the development of new biochemical techniques has intensified the search for other

protein hydrolysate Various combinations of the aminoacids leucine, isoleucine, threonine and valine also produced symptoms The patient was the result of a third pregnancy, the first two ending in miscarriages The results of glycine tolerance tests on his healthy parents were within normal limits

A preliminary report was recently published by McMurray *et al* (1962) on a new aminoaciduria, citrullinuria, in a mentally retarded boy aged 18 months whose parents are first cousins Freshly voided urine contained large quantities of this substance Chromatography showed no evidence of the presence of any other aminoacid in abnormal concentrations in the urine Citrulline metabolism in the child's relatives had not yet been investigated

#### HEPATOLENTICULAR DEGENERATION

This disease, first observed by Wilson (1912), is characterized by the progressive development of neurological symptoms, usually starting in adolescents or young adults Manifestations include rigidity, spasticity and tremors of the limbs Dysphagia, dysarthria and a fixed facial expression may develop Emotional deterioration is common and may culminate in dementia In a minority of patients, hepatic symptoms predominate and neurological features may be minimal or absent (Bearn, 1960) Pathologically, degeneration of the lenticular nucleus of the brain with cirrhosis of the liver is found

Affected individuals have substantially lower concentrations than normal of the protein, ceruloplasmin (Scheinberg and Gitlin, 1952) The level of this protein in the serum has little relationship to the duration or severity of symptoms Ceruloplasmin, normally present in the blood serum in the concentration of 30 mg per 100 c c, contains eight atoms of copper per molecule In Wilson's disease some failure of ceruloplasmin synthesis leads to deposition of excessive amounts of copper in the brain, liver, kidneys and other tissues, including, probably, the iris where a characteristic visible greenish brown ring (the Kayser-Fleischer ring) is produced Defective reabsorption in the kidney tubules results in generalized aminoaciduria in later stages of the disease

Bearn (1960) showed conclusively that Wilson's disease is recessively inherited There have, however, been suggestions

that more than one genetical type may be involved. The serum ceruloplasmin level of normal heterozygotes has not been found to be consistently abnormal. Sternlieb *et al.* (1961) measured the incorporation of a load of copper 64 into ceruloplasmin in cases of Wilson's disease, their parents and in normal controls; they suggested that this could provide a fairly reliable means of distinguishing heterozygotes.

The results of therapy have been variable. Prolonged administration of penicillamine, which increases urinary excretion of copper, has been the most successful method of treatment thus far (see Chapter XII).

### GALACTOSAEMIA

Galactosaemia, the first description of which appears to have been given by von Reuss (1908), is characterized by a specific enzyme deficiency the result of which is inability to convert galactose to glucose in the normal way. The defective enzyme concerned, gal-1-P-uridyl transferase, was first identified by Isselbacher, Anderson, Kurahashi and Kalckar (1956) using lysates of erythrocytes. The incidence of galactosaemia is unknown: about 100 cases have been reported.

Individuals affected with the disease seem to be normal at birth. Within a few days of beginning milk feeding, however, symptoms of varying severity appear. These can include vomiting, diarrhoea, lethargy, jaundice and failure to thrive. Hepatomegaly usually develops and the urine contains galactose. Aminoaciduria and proteinuria may also be present. Survivors are liable to suffer from cataract; mental retardation is present in a minority of them (Walker, Hsia, Slatis and Steinberg, 1962). Abnormalities appear only if the diet of affected infants contains galactose. A strictly galactose-free diet, instituted from birth, practically insures against the development of specific galactosaemic lesions. Diagnosis can be made at birth by incubating the new born infant's cord blood with galactose and showing an excessive accumulation of galactose-1-phosphate in erythrocytes (Schwarz, Holzel and Komrower, 1958).

Galactosaemia is inherited as an autosomal recessive trait. The first approach to the problem of partial enzyme defects in parents of galactosaemic children was made by Holzel and

Komrower (1955) They found that one or both parents of such children showed abnormal values in a galactose tolerance test. A more extensive subsequent survey with the oral galactose tolerance test (Donnell, Bergren and Roldan, 1959) showed that the test was unsatisfactory for detecting individual carriers because of considerable overlap in the range of values of normals and heterozygotes. Kirkman and Bynum (1959) compared transferase activities from normals and suspected carriers by using manometric determinations of oxygen consumption in haemolysates. Nearly an 80 per cent efficiency in carrier identification is achieved by this method.

### CRETINISM

A number of varieties of cretinism occur. In certain regions, iodine deficiency in the diet is thought to be responsible for goitrous cretinism and such cases are often referred to as endemic. In these cases, genetical predisposition could play a part in causation as only a proportion of the population in an endemic area is affected. Occasionally goitrous cretinism follows the ingestion of goitrogenic substances, such as thiouracil in a drug or cobalt. Other examples occur sporadically in circumstances where dietary iodine intake is adequate. Among these are individuals without goitre in whom the thyroid gland has failed to develop so that it is rudimentary or, in extreme cases, absent altogether.

There is also good evidence that, in many cases of so-called sporadic, or non endemic, goitrous cretinism, recessively determined metabolic defects in the synthesis of thyroid hormone occur. Hutchison and McGirr's (1956) report on an inbred family of Scottish tinkers left little doubt that cretinism can be the result of homozygosis for a particular gene, in these patients, cretinism was due to the absence of a dehalogenase. Several different types of metabolic block have been demonstrated in different families (Stanbury and McGirr, 1957) and they can reasonably be interpreted as being recessively inherited. Dysthyroidism of a comparatively mild degree, in near relatives of parents of cretins, might be taken as evidence for a slightly abnormal heterozygous disposition. McGirr, Hutchison and Clement (1959) demonstrated a defect in deiodinating monoiodotyrosine in several apparently healthy members of the

tinker family group which has already been mentioned, they were considered to be heterozygous carriers

Though cretinism has long been known, and frequently received special emphasis in discussions on mental defect, the condition is uncommon in hospital populations of defectives. In the past, cases of mongolism were often thought to be cretins and, in some countries, the term was applied to low-grade defectives in general. Among the clinical features, found in typical cases, are mental defect, sluggish behaviour, dwarfed stature, coarse dry skin and hair, and a large protruding tongue. An association with deafness occurs both in areas where cretinism is common, such as the Allgau district of Germany (Lang, 1929), and also among cases of familial goitre (Fraser, Morgans and Trotter, 1960).

#### RETINITIS PIGMENTOSA AND THE

##### LAURENCE-MOON-BARDET-BIEDL SYNDROME

Progressive degeneration of the retina, starting peripherally and giving rise first to reduced night vision and later on to optic atrophy and total blindness, is sometimes an uncomplicated condition. The dark pigmentation of the deep layers of the retina, which are exposed by the degeneration of the superficial structure, can be clearly seen under the ophthalmoscope. Possibly there is also a real enlargement of the pigment cells and Dax (1938) repeatedly demonstrated the presence of a melanophorotrophic substance in the urines of affected subjects. In an extensive survey of published cases, Bell (1922) found that severe disorder of the central nervous system, causing epilepsy, idiocy and other defects, was present in 37 out of 919 cases, or in 4 per cent. Wortis and Shaskan (1940) examined 41 new cases and reported mental defect in two of them.

The significance of the condition, from the point of view of mental subnormality, mainly depends upon its association with other abnormalities. One of the commonest peculiarities is deaf-mutism, another is polydactyly and a third is pituitary dystrophy. The retinal degeneration which occurs in some cases of spastic ataxia and also that in cerebromacular degeneration may sometimes be difficult to distinguish clearly from typical retinitis pigmentosa. It is not surprising that many different types of pedigrees of retinitis pigmentosa have been

found. In some the condition appears to be dominant and in others recessive. In some families partial sex linkage is a reasonable explanation and, in others, sex limitation. Not infrequently the disease seems to occur in an isolated case with no affected near relative. Evidently there are a number of different genes, or combinations of genes, which can produce similar effects.

The most important type of retinitis pigmentosa found in relation to mental defect is associated with both polydactyly and pituitary dystrophy. It was originally noticed by Laurence and Moon (1866), but Bardet (1920) and Biedl (1922) supplemented their description and the disease has become known as the Laurence-Moon-Bardet-Biedl syndrome. A comprehensive review of the subject has been made by Cockayne, Krestin and Sorsby (1935). These authors, in agreement with some others (Jenkins and Poncher, 1935), attribute the coincidence of so many peculiarities in the same patient to close linkage of two or more genes, concerned in producing the main constituents of the pathology. The theory is difficult to disprove; it cannot, however, be regarded as probable unless sibships can be presented in which the separate genes are seen to be in repulsion. For example, we need to demonstrate that sibships exist in which some members are affected with retinitis alone and others, without retinitis, have obesity and polydactyly. The supposition that it is impossible for a single gene to give rise to changes both in the ectodermal and mesodermal structures, which underlies the linkage theory, must not be taken as a basic biological principle.

The Laurence-Moon-Bardet-Biedl syndrome does not often cause very severe defect, though mental impairment seems nearly always to be present (Bell, 1958). The usual mental age is from 5 to 7 years. There is considerable variability both in the degree of defect and in the physical signs, even among several affected members in the same sibship. Furthermore, although there is little doubt that the inheritance is recessive, the gene is not completely recessive. Close relatives, who may be heterozygous carriers, occasionally show some slight sign, such as polydactyly or obesity. For example, in the family recorded by Griffiths (1931), there were at least two children affected and three normal. The mother was obese and her



brother was polydactylous. The patients of Ellis and Law (1941) only had infantilism and retinal dystrophy, but again a maternal uncle had polydactyly. A typical example of the syndrome is shown in Plates IIIa and IIIb.

#### AMAUROTIC IDIOCY

Congenital, infantile, late infantile, juvenile and adult forms of amaurotic idiocy have been described. It is doubtful how far they are all separate diseases. They are all conditions in which there is recessively inherited disturbance of lipid metabolism. Infantile and juvenile amaurotic idiocy are the two best known types.

Infantile amaurotic idiocy, also known as Tay-Sachs disease, was first described clinically among an inbred Jewish population in London by Tay (1881) and the pathology was examined by Sachs (1886). Most cases have been found in Jewish families, though Hanhart (1943) reported several instances in the population of Switzerland, and Komai (1934) noted the condition among Asiatics. The disease is extremely rare. Slome's (1933) analysis of published sibships clearly indicates that it is due to a single autosomal gene in spite of a slight excess of female cases. The proportion of cases with first-cousin parents ranges from 11 to 40 per cent in different populations. Clinical features first appear at the age of a few months in a previously healthy infant. These symptoms are nystagmus and a loss of voluntary movement. The ophthalmoscope reveals the presence of a brownish red spot in the macular region in the fundus. In the course of a year or so the condition advances to a state of profound idiocy, with paralysis, complete optic nerve atrophy and blindness (amaurosis); death usually occurs before the age of 2 years. The cerebral pathology consists of a degeneration first of the nerve cells of the pyramidal system and later of all the other nerve elements. This appears to be due to a biochemical deficiency which prevents the body from utilizing certain essential lipid constituents of the brain cells. The nerve cells of the brain contain abnormal accumulations of pre-lipoid substances (Schaffer, 1925) and substances resembling neutral fat in their staining reactions are found within and between the cells. No biochemical abnormalities have been noted in the urine, blood or cerebrospinal fluid.

condition, similar to Morquio's disease, has been reported to be inherited as a heterozygous irregularly dominant disease (Shafar, 1941)

Another condition, known as Gaucher's disease, is characterized especially by visceral lipid deposits. In the Hand Schuller Christian syndrome, dwarfism and pituitary obesity can be combined with deposits in the bone marrow. The osseous deformities of gargoylism and Morquio's disease probably also have their origin in similar dystrophic processes.

Disorders of lipid metabolism occur in a large group of diseases, extending from osteochondrodystrophies to macular degenerations, and a number of others such as xanthomatosis of the skin, not relevant to the study of mental defect. It is convenient to group them together for purposes of systematic pathological classification, just as we can group together phenylketonuria and alkaptonuria. The various lipid disorders are not proved to be genetically related to one another, though, of course, it is possible that they could represent the effects of a series of allelic genes. Different genes can produce the same type of end result by quite different mechanisms because the metabolism of a given essential substance in the body can be disturbed in a variety of ways.

#### CEREBRAL DIPLEGIA

Symmetrical spastic paralysis chiefly affecting the lower limbs, is an important and not very infrequent symptom found in conjunction with mental defect. It can occur in a large variety of diseases and has many different causes. In the cases originally described by Little (1843), paralysis of cerebral origin, bilateral and fairly symmetrical in distribution was the predominating or perhaps the only symptom. It is present at birth and is usually first noticed at about the age of 6 months or later. Neurologically the condition is almost stationary, though it may appear to worsen with age in consequence of muscular contractures. Sometimes it becomes accentuated after specific fevers (Dawidenkow, 1926).

The legs are most severely affected, but other parts of the body also suffer. When all four limbs are seriously involved, the term quadriplegia is applicable. Commonly there is some involvement of the facial muscles, which tend to overact

when speech is attempted. The legs tend to assume a stiff scissor-like posture and the feet assume a flexed position, so that the subject who learns to walk has to do so on his toes. When paralysis affects the arms, the hands are held with flexed wrists and the fingers can be hyperextended. In typical cerebral diplegia, all tendon reflexes are brisk, particularly in the legs. There is increased tone in the muscles of affected limbs and the plantar responses are extensor. The abdominal reflexes are usually present.

Mental defect is not an invariable accompaniment, but there is a positive correlation between the severity of the neurological symptoms and the degree of intellectual impairment. On careful examination, however, patients physically handicapped by cerebral diplegia are found to be more intelligent than at first expected. After testing all cases in a sample of over 100 diplegic and hemiplegic children, McIntyre (1938) reported that only 18 were defective and 21 others were of dull or borderline intelligence (see also Table V, p. 39). Emotionally they have a tendency to be cheerful and even euphoric. Hospital cases may be of any grade, but imbeciles predominate. The sexes are affected with equal frequency.

The pathological lesion in the majority of cases must be primarily related to the pyramidal system, but it may be very difficult to demonstrate any characteristic changes in the cerebral cortex, either macroscopically or microscopically. In some cases there may be lesions in the basal ganglia, particularly in the caudate nucleus, the putamen and the globus pallidus. The average size of the head is not diminished as compared with that of other individuals of the same mental grade. As the condition is not by its nature progressive, one explanation is developmental abnormality associated with absence, rather than degeneration, of certain nerve tracts. Furthermore, cerebral diplegia is sometimes accompanied by congenital malformation, such as club foot or dislocation of the hip (Wollenberg, 1909).

The original hypothesis of Little, that congenital cerebral diplegia was due to injury or to asphyxia at birth, has not received much support from neurologists in the past, partly because paralysis due to cerebral trauma or infection would be unlikely to affect both sides of the body equally. Nutritional

deficiency at an early period of intrauterine development is credited by Stewart (1942) as the cause of some cases. Anoxia during the process of birth is now believed to be an important cause of symmetrical cerebral lesions. This view has been upheld in particular cases on clinical grounds by Evans (1948). The wholesale ascription of all types of infantile cerebral palsy to birth trauma, as implied in the work of Doll, Phelps and Melcher (1932), cannot be accepted as valid. There are many instances where the condition has all the characteristics of recessive gene determination (see Figure 10). Parental con-

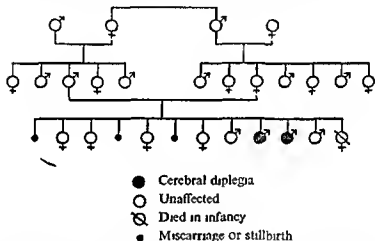


Figure 10 —Pedigree of two brothers with spastic diplegia. The elder had very slight signs and was normally intelligent. The younger was typically diplegic with a Binet I Q 72 (Colchester Survey 1938, Case No. 333).

sanguinity and affected sibs have been frequently reported (Book, 1949). Hanhart (1936) found seven cases in four related sibships, in which all the eight parents had a common ancestor, born in the seventeenth century. Spastic diplegia, with ichthyosis and mental deficiency, has been shown by Sjogren and Larsson (1957) to be recessively inherited.

Though in the majority of diplegias the predominant clinical signs indicate defect of the pyramidal tracts, many cases show signs also of involvement of the extrapyramidal system. A few cases, moreover, have mainly or exclusively signs of extra-

pyramidal lesions. These extrapyramidal symptoms are peculiar squirming movements and contortions which are evident as soon as voluntary action is attempted. Slight athetotic signs are often found associated with diplegia, especially in the face, but the extreme picture of choreoathetosis is so characteristic that it warrants being considered as a separate condition. Moreover, in severe cases of choreoathetosis, signs of pyramidal disease, such as permanently increased muscular tone and extensor plantar responses, may be absent. Deafness is sometimes an additional complication. The mental grades of cases with extrapyramidal rather than pyramidal signs, though distributed widely over the whole range from normal capacity to idiocy, are somewhat higher than the average for all diplegics (see Appendix 8). Male and female cases are found in about equal numbers.

As with specifically pyramidal diplegias, the neurological signs in athetotic cases do not show a tendency to progression, though disabilities secondary to abnormal muscular action may increase with age. Pathological changes in the basal ganglia are to be more confidently expected when athetosis is present than when it is absent.

The causes of choreoathetosis, again, are multiple, foetal malnutrition and anoxia are not ruled out. Indeed, Norman (1947) considers that the peculiar condition of unevenly distributed hypermyelination of nerve fibres, associated with areas of 'marbling' in the basal nuclei, which is sometimes found post mortem, is due primarily to asphyxia at the time of birth. Another important cause can be neonatal jaundice due to lysis of blood cells on account of maternal and foetal antigenic incompatibility (see Chapter X). There are also cases of diplegia, with predominantly extrapyramidal symptoms, which are examples of recessively determined defect.

#### FRIEDREICH'S ATAXIA

Allied to the cases of congenital diplegia are those which come under the heading of paraplegia, in which the lower limbs only are affected. The group of paraplegias, however, of which Friedreich's ataxia first described in 1863, forms an important example, are progressive diseases. The onset is delayed until physical and mental development are completed

in the majority of cases and, thus, if associated mental deterioration takes place, the condition is usually described as dementia rather than as amentia. Friedreich's disease and the recessive types of spastic paraplegia according to Bell and Carmichael (1939), begin, on the average, at the ages of 12 years and 15 years respectively. Though the degenerative lesions are primarily in the spinal cord, occasionally mental defect is an accompaniment and, for this reason, these conditions can sometimes be found among inmates of hospitals for defectives.

The cardinal signs of Friedreich's ataxia are loss of deep reflexes in the legs, extensor plantar responses and pes cavus deformity, associated with ataxia and nystagmus. Sense of position and vibration are lost in the legs and sometimes also in the arms (Saunders, 1914). Mental defect must be classed among the associated anomalies which include scoliosis, spina bifida, digital malformation and degeneration of the optic nerve. Retinal degeneration is a rare accompaniment, but its occurrence in sibships closely related to those containing cases of Friedreich's ataxia led Franceschetti and Klein (1947) to postulate a common genetical background for the two conditions.

The recessive nature of the majority of cases of Friedreich's ataxia is established by the fact that all parents are unaffected and that there is sharp segregation of the affected and unaffected children. Moreover, about 10 per cent of the recorded cases have first cousin parents. The same holds true for the allied disease, recessive spastic paraplegia, in which the clinical signs are quite similar, with the exception that deep reflexes are present and may be exaggerated. Another recessive trait connects mental defect of high grade type with cataract and cerebellar ataxia (Garland and Moorhouse, 1953) in the offspring of first cousins.

#### MICROCEPHALY

Few descriptive terms in medicine have more vagueness than the diagnosis of microcephaly. Any cranium noticeably below the average size, appropriate to the age and sex of the subject, can be called microcephalic. One clinical tradition, without specifying age, confines the description to heads measuring less than 13 inches in circumference. This measurement, according to the phrenologist F. J. Gall, represents a minimum below

which idiocy is inevitable. A variety of cases with small heads occurs. The head may be well-proportioned with the rest of the body, though smaller than usually found in the general population, or it may be disproportionately small. Smallness of the head is common in many types of mental defect, such as mongolism and phenylketonuria, and in many other patients who do not belong to any recognizable type. A small head can result from imperfect brain development caused in a number of different ways. An important group of cases is caused by

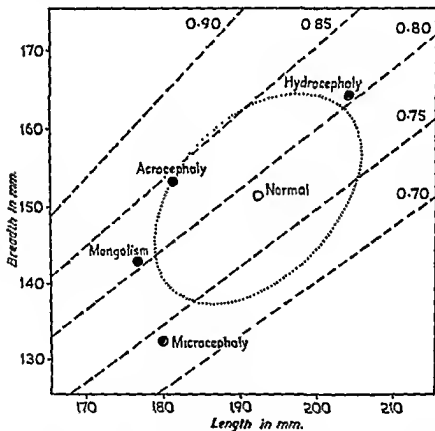


Figure 11.—Mean head length and head breadth in adult males.

Dotted line indicates the normal limits of measurements 95 per cent are within the ellipse. Levels of cephalic index are shown by broken lines. Note that the means of the four types of patient are outside the normal range. The cephalic index in acrocephaly and mongolism is high and, in microcephaly, it is low.

irradiation early in pregnancy Among persons with absolute, though not relative, reduction of head size are also dwarfs with normal intelligence In African pygmies, reduced head size can occur normally together with reduction of body size (Schebesta and Lebzelter, 1933)

Abnormally small heads can be separated from the normal by actual measurement, if suitable norms are provided, but the shape of the head is also important A class of cases can be clinically distinguished from the rest of defectives by the fact that the head is diminished greatly in the vertical measurement and in width but is less abnormal in length These dolicocephalic cases (i.e. those with low cephalic index) can be fairly well distinguished from the rest (Figure 11) By limiting the term "microcephaly" to this class, mongols, acrocephalics and other defectives who may have small heads of quite different shapes can be excluded (see Table XXXI) The group of relatively long headed microcephalics includes a type which is caused by a single recessive gene and which has been termed "true microcephaly"

Recessive true microcephaly is a highly characteristic condition Patients are invariably below the average stature They are usually active and physically fairly healthy The rest of the body, though dwarfed, is often well developed, it contrasts with the head size by its relatively normal musculature and sexual organs Some of these patients make quick, furtive movements which, together with their stooping posture, are reminiscent of some of the lower animals, and they were called "bird men" by Lombroso The face is not so much reduced in size as the head, so that a relatively normal nose, chin and large ears may contrast with the receding forehead and low vertex in a manner reminiscent of the popular idea of a criminal type These peculiarities were alleged by Langdon Down to constitute an Aztec type of defect Psychologically, true microcephalics, found in hospitals for the mentally subnormal, are usually of the low imbecile grade Though reputed to be querulous and bad tempered if well treated they are among the happiest and most harmless of patients A case is illustrated in Plates IVa and IVb

Familial cases of true microcephaly were reported by Barr (1904) and cousin parents were noted by Shuttleworth (1875)



A pedigree given by Hanhart (1943) showed ten interrelated cases with parental consanguinity in two sibships. Halperin (1944) described three instances of affected sibs with normal

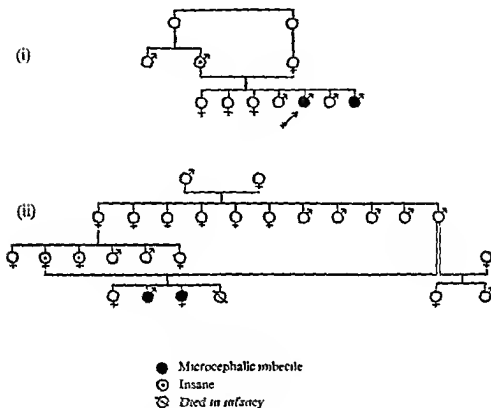


Figure 12.—Two pedigrees of recessive microcephaly

- (i) The father of the two microcephalics suffered from a paranoid psychosis at the age of 41. The arrow indicates the patient shown in Plates IVa and IVb
- (ii) The family is from the Colchester Survey 1938 (Case No 942). The mother and aunt of the microcephalics suffered from manic depressive psychosis (Penrose 1938a)

parents. Familial incidence and a high rate of parental consanguinity has been noted in Japanese cases by Komai, Kishimoto and Osaki (1955) and in Dutch cases by van den Bosch (1959). Altogether, the familial incidence seems to be a little

lower than would be expected if all cases were due to recessive genes and there may be other causes for conditions which are clinically very similar. Most of the parents of microcephalics seem quite normal, but mental diseases and defects are found in some. Whitney (1930) reported a sibship which contained six cases of microcephalic imbecility, one sib and both parents were not microcephalic but were mentally defective. Psychosis appeared in one parent of microcephalics in both the pedigrees given in Figure 12. As in phenylketonuria, there is a possibility that the gene may predispose the heterozygous carriers to mental abnormality. The gene frequency of recessive true microcephaly has been estimated, by Book, Schut and Reed (1953), as between  $1/162$  and  $1/230$  in the Swedish population. The estimate of Komai, Kishimoto and Osaki (1955), for the Japanese population, agreed closely with these figures.

The brain in recessive true microcephaly is extremely small and may weigh less than 1000 g. The cortical convolution pattern is much simplified. In consequence of the small cerebrum, the cranial vault shows premature synostosis and considerable thickening as compared with the normal. As pointed out by Shuttleworth (1875), the skull peculiarities are not the cause of the brain defect, as originally supposed by Virchow, but a secondary effect of the small brain. If an anthropologist should find a skeleton of a microcephalic, he might well conclude that it had belonged to a species different from *homo sapiens* though closely related. It is remarkable that a single gene can produce such a gross change, compatible with life if not with normal fertility.

#### MISCELLANEOUS RECESSIVE ABNORMALITIES

Among the types of low-grade defect there are undoubtedly many rare, recessively determined diseases. Some of these have only been infrequently described and others still remain undetected. In an extensive survey of a peasant population in Sweden, Sjögren (1932) was able to discover a large number of imbeciles in related families. The tendency for more than one sib to be affected, together with the demonstration of common ancestry in many instances, convinced him that the cases were due to a recessive gene, although no specific pathology could be found. There were considerably more male than

female imbeciles in the group, i.e. 34 against 18, a disparity for which no satisfying explanation was advanced. Sharp segregation was found between the normal and abnormal sibs with respect to mental grade and 6 per cent of the sibships had consanguineous parents. Though it is quite possible that a single gene, causing a hitherto undetected metabolic disturbance, might be the cause of all these cases, it is also conceivable that more than one type of disease was included in the sample. The estimated true ratio of affected to total sibs was significantly less than one quarter. Moreover, in isolated communities the interpretation of a high parental consanguinity rate as evidence for recessive determination presents difficulties. For example, in the general population of one north-Swedish district, investigated by Book (1948), the proportion of first cousin marriages was nearly 7 per cent.

The association of deaf-mutism with parental inbreeding, observed by Boudin (1862), has been amply confirmed by Hanhart (1943) who has convincingly demonstrated that recessive genes could be the sole determining factors in a large number of pedigrees. Subjects with deaf-mutism are only occasionally mentally defective. According to Lindenov (1945), feeble-mindedness is a complication only when retinitis pigmentosa also is present.

Recessive inheritance is likely in a number of conditions, in addition to those discussed already, in which mental defect is associated with ocular abnormalities. For example, Kallman, Barrera and Metzger (1940) recorded a sibship containing four microphthalmic children of whom three were imbeciles and the parents were cousins. Sjogren (1935) described 40 defectives suffering from congenital bilateral cataracts in 30 sibships. The combination of cataract and mental defect was obviously not fortuitous, and two sibships had first cousin parents. Two sibships with defectives suffering from keratosis of the hands and feet were recorded by Hanhart (1947), one of the patients had a corneal dystrophy also. Recessive inheritance is suggested also for two defective sibs with a peculiar form of retinal pigmentation, associated with dwarfism and deafness, described by Cockayne (1936, 1946). Similar findings were reported in another pair of sibs by Neill and Dingwall (1950) who thought that the condition was allied to progeria.

One type of congenital methaemoglobinaemia, likely to be recessive, is associated with severe subnormality (Hitzenberger 1933) Gibson's (1948) studies show that the missing factor can be an accessory co-enzyme necessary for methaemoglobin reduction in the erythrocytes Cyanosis and compensatory polycythaemia may occur. Treatment of the methaemoglobinaemia by administration of ascorbic acid (Deeny, Mundrik and Rogan 1943) or methylene blue has achieved good results, but no intellectual improvement appears to take place with such therapy

A family has been described by Richards and Rundle (1959) in which severe subnormality was associated with the excretion of abnormal ketosteroids in three sisters and a brother Other findings include underdevelopment of secondary sex characters, deafness, ataxia and peripheral muscular wasting One brother, with similar symptoms, died before biochemical investigations could be undertaken The parents, who were second cousins, also had eight normal children It is probable that the condition is recessively inherited

An evidently recessive type of mandibulo-facial dysplasia was described by Jancar (1961) with mental deficiency as an associated symptom The morphology of the head in these patients resembles superficially that found in 17 or 18 trisomy (see p 220) but no abnormality was found in the chromosomes of one of the two affected brothers available for testing

## CHAPTER VIII

### SEX CHROMOSOME ANOMALIES, SEX LIMITATION AND SEX LINKAGE

*General Principles—Sex Chromosome Aberrations in Females—Sex Chromosome Aberrations in Males—Aetiology of Sex Chromosome Aberrations—The Y Chromosome—Sex Limitation and Sex Linkage—Muscular Dystrophy—Oculocerebrorenal Syndrome—Nephrogenic Diabetes Insipidus—Anhidrotic Ectodermal Dysplasia—Hydrocephaly—Miscellaneous Pedigrees—The Biology of Sex Limitation and Sex Linkage*

#### GENERAL PRINCIPLES

FROM the biological point of view sex is an inherited trait. The normal male has received an X-chromosome from his mother and a Y-chromosome from his father, the normal female has received one X-chromosome from each parent. There are three, possibly four, kinds of hereditary variation connected with sex. First, there are the normal differences between the sexes, expressed in the morphology and function of the gonads and also in secondary sex characters. These traits depend upon correct balance of sex chromosomes and autosomes; they can be altered if there are peculiarities of the sex chromosome complement or if there are certain abnormal genes present on any chromosomes.

Secondly, there are hereditary traits determined by autosomal genes which are manifested differently in the two sexes. This phenomenon is called sex influence or sex limitation. Thirdly, there are true sex-linked characters determined by genes located on the X chromosome and which, consequently, have a very special hereditary pattern. There is a possible fourth category of traits caused by genes on the Y chromosome which, consequently, would be transmitted only from fathers to sons; no traits of this kind, associated with mental deficiency, are known.

Besides the differentiation of genetical sex by chromosomal

analysis there is a method which uses the resting nucleus. Barr and Bertram (1949) discovered that each female cell nucleus contained a small, darkly staining, body lying close to the boundary membrane and which was not found in male cell nuclei. The Barr body, which is believed to be composed largely of DNA and was first seen in cerebral cells of cats, can be seen easily in human epidermal tissues. The standard method is to make a smear of desquamated buccal mucous membrane. In a specimen from a normal female, cells which are not autolysed show one Barr body in a fair proportion of nuclei, i.e. from 10 to 40 per cent. The method is of particular interest, in all cases where an aberration affecting the X chromosome is suspected, because the Barr body seems to depend upon the presence of more than one X. In the male with only one X there is no Barr body, the normal XX female has one body and when there are three X chromosomes present, two bodies are visible in many cells. Further, in diploid cells with four X chromosomes three Barr bodies can sometimes be seen. These points are



Figure 13—Diagram of epithelial cell nuclei showing sex chromatin bodies in different types of patient

- (a) Normal male or Turner's Syndrome
- (b) Normal female or XXY Klinefelter
- (c) Triple X female or XXXY Klinefelter
- (d) Quadruple X female or XXXXY Klinefelter

demonstrated diagrammatically in Figure 13. It has, moreover, been observed in some cases, where a defective or deleted X chromosome is present, that there is an unusually small corresponding Barr body.

The relationship between an X chromosome and the production of a Barr body is not yet understood. A theory current at the present time, which is strongly supported by Ohno and Makino (1961), is that this body always represents a single X, which is in a state of "precocious condensation", and that a complete set of 22 pairs of autosomes suppresses the process

in one and only one X. It is, moreover, considered likely that the entry of a given X chromosome into this state of precocious condensation implies that the particular chromosome involved is inactive genetically at that time. The existence of specific differences in the segmentation of polymorphonuclear leucocytes has been established by Davidson and Smith (1954) but their relationships to chromosomal anomalies is even less clear than those of the Barr bodies

#### SEX CHROMOSOME ABERRATIONS IN FEMALES

A type of ovarian dysgenesis, associated with diminished stature, webbed neck, imperfect extension of the elbows and cardiac malformation, is known as Turner's syndrome. These patients, when they are of the standard type, have no Barr sex chromatin bodies in their cell nuclei. Mitotic cells show that the total number of chromosomes is 45, that there is only one X present and no Y. The intelligence level does not appear to be much affected by this disturbance though subjects may be occasionally subnormal. More often they are physically weak on account of circulatory inadequacy.

The complementary peculiarity is known as the triple-X female, sometimes called superfemale, because three X chromosomes are found among a total of 47 (Jacobs, Baikie, Court Brown, MacGregor, Maclean and Harnden, 1959). Cells of these patients often show two chromatin bodies. Physically they are not necessarily distinguishable from normal females though, in some instances there is delayed or absent menstruation. Mentally, however, they tend to be subnormal, usually in a mild degree, with I.Q. above 50, though severe cases are known. The most typical accessory clinical findings in low grade patients with triple-X seem to be epilepsy and increased muscle tone. When they are fertile their offspring have been found to be normal (Fraser, Campbell, MacGillivray, Boyd and Lennox 1960) although a tendency to produce triple-X daughters would seem a likely possibility. Mentally defective females with probably four X chromosomes and a total of 48 chromosomes have been described, some of whose cells contain three Barr bodies. Carr, Barr and Plunkett (1961) described two such patients with I.Q. 30 and 50 respectively but no notable physical defects.

There are numerous types of females with sex chromosome aberrations besides those already mentioned. For example, Turner or triple-X patients can be mosaics with a considerable portion of their cells normal. It is possible for the same individual to be partly Turner and partly triple-X (Jacobs, Harnden, Court Brown, Goldstein, Close, MacGregor, Maclean and Strong, 1960). Another peculiarity is the presence of either a partially deleted or an enlarged and distorted X chromosome. An important variant is produced by the junction of two long arms of X chromosomes at the centromere to form one symmetrical large chromosome, called an isochromosome X, which looks very much like No. 3 (Fraccaro, Ikkos, Lindsten, Luft and Kayser 1960). A female with one normal and one isochromosome X tends clinically to resemble a case of Turner's syndrome, and this suggests that the shorter arm of the X, which is lost in the isochromosome, is more active than the longer one. Yet another anomaly is the result of simultaneous breakage of small fragments off both ends of an X chromosome and subsequent rejoining of the ends to form a ring. This very rare phenomenon was found in many cells of a patient described by Lindsten and Tillingier (1962). A large ring chromosome is bound to be unstable because of the topological results of strand crossing in reproduction, rendering breakage or non disjunction inevitable during meiosis. Again, the clinical type resembled the Turner syndrome.

Finally, it should be emphasized that numerous cases of ovarian dysgenesis and others with abnormal secondary sex characters, when investigated cytologically, are found not to have any noticeable deviation from the normal female karyotype.

#### SEX CHROMOSOME ABERRATIONS IN MALES

In males a series of sex chromosomal anomalies has been found similar in some respects to those in females, the exception is that here every patient has at least one Y chromosome (see Figure 14). The possession of two Y chromosomes is compatible with normal development and fertility (Hauschka, Hasson, Goldstein, Koepf and Sandberg, 1962) but the association of even one Y with two X chromosomes produces abnormality. The type XXY is found in many patients who exhibit



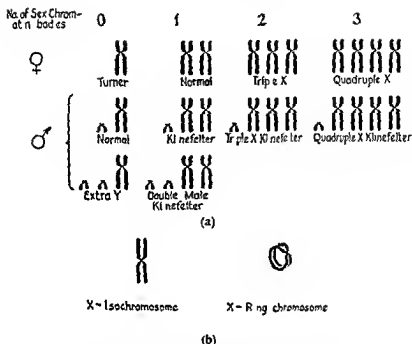


Figure 14 —Diagram of sex chromosomes

- (a) Normal and eight abnormal complements classified by sex  
 (b) Two abnormal X chromosomes

**the Klinefelter syndrome** These are males who develop fairly normally until puberty. At this point testicular atrophy sets in and some degree of feminization. The voice is typically high-pitched, there is only slight hair on the chin and in the armpits and gynaecomastia is common. These patients tend to be tall and slender in build, mild in manner, and subnormal intellectually. When adult, they have increased excretion of follicle stimulating hormone. The syndrome, first described by Klinefelter, Reifenstein and Albright (1942), which these patients exhibit is not a single disease entity. Patients clinically indistinguishable may be found to have quite different karyotypes in their cells. Less than half the male patients so diagnosed have normal XY sex chromosomes and, correspondingly, absence of Barr chromatin bodies in their resting cells (Miller 1961). Those who have Barr bodies present usually have XXY sex chromosomes, however, occasionally they may have XXXY

sex chromosomes (Ferguson-Smith, Johoston and Handmaker, 1960) with double chromatin in some cells, or even XXXXY (Carr, Barr and Plunkett, 1961) with triple chromatin. Another variant is what may be termed the double male with XXYY complement of sex chromosomes and single Barr bodies. Numerous mosaic types with a proportion of their cells normal are also known.

There does not seem to be any clear physical distinction between these various types. They all show the same kind of testicular atrophy but there is much variation of body build, stature and manifestation of feminine characters within each karyotypic group. Dermal ridge patterns on the palms of the hands are not unusual in most cases though they tend to show a rather vertical alignment, a trait which is the opposite of that shown in mongolism.

The mental state of male patients with more than one X chromosome varies from a normal intellectual level to idiocy. It is difficult to establish the true distribution of intelligence because unselected samples can only be obtained soon after birth. Patients who are first seen at fertility clinics are likely to be of average ability and their numbers are not easily ascertained. Those who are found in mental deficiency hospitals, however, are mainly in the mildly subnormal class (Ferguson-Smith, 1958). Moreover, patients with one Y chromosome and three or four X chromosomes are not necessarily of lower mental level than those who have only an XXY set. There is general agreement that these patients have quiet dispositions; they are cooperative and willing but rather seclusive and at times mildly paranoid.

#### AETIOLOGY OF SEX CHROMOSOME ABERRATIONS

By investigating the sex chromatin in buccal mucosa cells of infants at birth, the incidence of the commonest types of sex chromosome anomalies can be inferred. Large scale surveys were made by Moore (1959), Bergemann (1961a) and Macleao, Harnden and Court Brown (1961). The results when pooled show 18 instances of female sex chromatin, probably Klinefelter cases, among 6801 male births, a frequency higher than 1/400. Two sex chromatin-negative females were found in 6641 female infants, suggesting an incidence of 1/3000 for

Turner's syndrome Double sex chromatin in a proportion of cells was found, by Maclean *et al*, in four females out of 3000 examined as three of these were shown to be XXX females the incidence of this peculiarity in the population is probably at least 1/1000 Comparing the population incidence of Klinefelter's syndrome with estimates of nearly 1/100 in samples of defective males, the condition is seen to be definitely associated with mental retardation although the majority of patients must pass as normal in this respect The same argument applies also to XXX females

Evidence concerning familial incidence of sex chromosome aberrations is not impressive The presence of two cases of the same or of different kinds in a sibship is a very rare event Boyer, Ferguson-Smith and Grumbach (1961) found no example in a series of 70 cases of Turner's syndrome

Direct transmission of the single X condition from mother to daughter is never likely to occur because of the extreme degree of infertility of Turner patients and considerations of the same kind apply to XXY Klinefelter patients The triple-X females, nevertheless, are not specially infertile Several normal offspring of an affected female have been reported by Stewart and Sanderson (1960), transmission of the triple-X condition from mother to daughter has been reported by Bergemann (1961b)

Some fairly comprehensive studies have been made concerning the question of maternal age in relation to patients with X-chromosome aberrations Lenz, Novakowski, Prader and Schirren (1959) found a definite increase above the average for maternal age in Klinefelter's syndrome but no appreciable similar effect in Turner's On the other hand, triple-X females show a significant tendency to occur at late maternal ages, when available data are pooled, though the effect, here, as with the Klinefelter syndrome, is much less obvious than in mongolism

These maternal, and possible paternal, age associations agree with the suggestion that the causation of the standard sex chromosome anomalies have their origins in non disjunctional errors which are liable to take place during gametogenesis Most of them could arise from unbalanced, haploid, mature ova, carrying either no X or as many as three X chromosomes, fertilized by a normal sperm with a single X or Y When there

IV p 84) Subsequent investigations have not provided much support for this view and there is no indication, from cytological observations, that the X and Y chromosomes pair with one another, in the manner of homologous autosomes, during germ cell maturation. Thus characters controlled by genes on the Y chromosome have a very special kind of inheritance in that they are transmitted by the father to all sons. Its most important function in man is to determine that the gonads are testes. Otherwise no genes have been allocated with certainty to the Y chromosome, except possibly one causing hairs to grow on the ears (Dronamraju, 1960). In some families Y chromosomes recognizably larger than normal have been shown to be inherited from father to son. Duplication of Y can take place without necessarily causing abnormality, as previously mentioned.

#### SEX LIMITATION AND SEX LINKAGE

The study of sex-limited traits, which are manifested differently in the two sexes although they depend upon autosomal genes, is of considerable interest in the field of mental deficiency. The larger range of variation in males than in females for general intelligence is an outstanding phenomenon. Physical measurements, such as stature, head size, weight and dermal ridge pattern quantity, also have different means as well as different ranges in males and females. With such metrical traits as these sex limitation can be distinguished from sex linkage by comparing correlation coefficients in various types of pairs of relatives, as explained in Chapter V p 111. Herrmann and Hogben (1933) showed that brother-brother and sister-sister coefficients for intelligence were higher than those for brother-sister pairs which suggested that sex-linked genes were determinants of the character. However, Willoughby (1928) calculated parent-child correlations of the four different types and was unable to demonstrate any tendency towards the pattern produced by sex-linked factors. The equivalent test, made by comparing the mental grades of offspring when parental levels differ, leads also to the conclusion (see Chapter IV p 83) that sex-linked genes do not have a detectable influence on multifactorial quantitative variations.

Rare segregating traits, which are associated with severe

mental and physical disease, nevertheless have a very characteristic pattern of inheritance which is usually interpreted as the result of the transmission of an abnormal gene on an X chromosome. All affected individuals are males and transmission is through unaffected females. If the males are so severely affected that they never become fathers, there may be no way of telling whether the trait which shows the hereditary pattern is sex-limited or sex-linked. This is because the critical pedigrees, in which an affected father fails to transmit the trait to his sons, which are the hallmarks of X chromosome inheritance, can never appear. If, however, females who carry the gene can be detected reliably, the theory of gene frequency can be used as the basis of a test to distinguish between sex limitation and sex linkage.

For sex-linked inheritance, the genotypes and phenotypes and their frequencies in a population under random mating conditions can be shown thus, where  $p+q=1$ :

Genotype	Males Phenotype	Fre- quency	Genotype	Females Phenotype	Fre- quency
$A$	Normal hemizygote	$p$	$AA$	Normal	$p^2$
			$Aa$	Normal or slightly affected	$2pq$
$a$	Affected hemizygote	$q$	$aa$	Affected	$q^2$

If  $q$  is very small, as will be the case when  $a$  is a rare type of abnormal male,  $q^2$  will be very small indeed and  $aa$  exceedingly rare. However, the heterozygous females  $Aa$  will be twice as frequent as the affected males  $a$ , for  $p$  will almost equal unity. Thus, if the heterozygous females are reliably detectable and if they are found to be twice as frequent as the affected males, the theory of sex-linked inheritance of the condition concerned can be fairly confidently asserted.

In quite a number of examples of sex-linked inheritance the heterozygous females can be detected by special tests, as in glucose-6-phosphate dehydrogenase deficiency (Childs, Zinkham, Browne, Kimbro and Torbert, 1958). Even so, there is a

greater variability in heterozygous females than in affected hemizygous males. Sometimes the heterozygous female has merely a very mild manifestation of a trait which is severe in males, as in chorioidal degeneration (Falls and Cotterman, 1948) and ocular albinism (Waardenburg, 1932). When there is also much variation in the phenotype of the affected males the diagnosis of X chromosome inheritance becomes less certain because it is not possible to make sure whether or not a male parent or other relative is affected. This kind of doubt arises in pedigrees of non specific mental retardation, which appears to be sex linked, as that described by Martin and Bell (1943), or which appears to be sex limited as in the pedigree described in Losowsky (1961).

The most reliable method of deciding between sex linked and sex-limited inheritance depends upon the ascertainment of genetical linkage, between the trait concerned and other markers, known to be on the X chromosome. With regard to two fully accepted cases of sex linkage, colour-blindness and haemophilia, the knowledge that the causal genes are fairly closely linked (Haldane and Smith, 1947) helps to establish their locations on the X chromosome. New information is rapidly being obtained about other loci by using the Xg blood antigen as a marker (Mann, Cahan, Gelb, Fisher, Harper, Tippet, Sanger and Race, 1962). Eventually the supposed location on the X chromosome of genes which are responsible for rare cases of mental defect, may also be established or disproved by testing for linkage with one or more of these marker traits.

As with abnormal genes situated on the autosomes, all those on the X chromosomes must have originally arisen by mutation. If a sex-linked gene causes lowered fertility in affected males, it will tend to be eliminated from the population, at a rate which is intermediate between that for a dominant and that for a recessive defect but nevertheless quite rapid. Provided that the heterozygous female carriers are no more, and no less, *fertile than females in the general population*, the mutation rate can be estimated, from a knowledge of the frequency and fertility of diseased males, in the manner described by Haldane (1935). For all kinds of haemophilia taken together, the rate is about one in 50 000 per X chromosome per generation. For

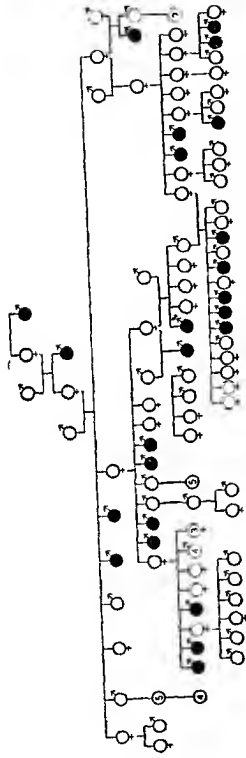


Figure 16 — Pedigree of muscular dystrophy with imbecility showing supposedly sex-linked type of inheritance (Allen, Herndon and Dudley 1944).

each separate type the rate could be less than this, particularly in the mild varieties. In the extreme case of a rare sex-linked lethal, like one sort of hydrocephaly, the mutation rate per X chromosome per generation is almost one third of the incidence of the disease in the male population.

#### MUSCULAR DYSTROPHY

A mild degree of mental retardation is sometimes found in association with the sex linked or Duchenne type of pseudohypertrophic muscular dystrophy. Classically, these patients are young boys in whom there is initially fibrous enlargement of several muscles, notably in the calves, which is soon followed by wasting. Great physical disability ensues and the intelligence level may be misjudged by mental testing. In consequence of the muscular degeneration, large amounts of creatine are excreted in the urine.

*Heterozygous females who can transmit the causal gene are healthy but may show slight indications of muscular hypertrophy or of latent degeneration detectable only by electromyography (van den Bosch, 1960).* In one instance, a female with gonadal agenesis who probably had a single X chromosomal constitution, was found to be affected as severely as is usual in the hemizygous male (Walton, 1956). Tests for genetical linkage, in families which contain individuals with sex-linked traits, show that the locus for this type of muscular dystrophy is not very close to that for colour-blindness and that it is even further away from that for the antigen Xg.

An excellent example of a typical pedigree, which can be interpreted traditionally as demonstrating sex-linked inheritance, was recorded by Allen, Herndon and Dudley (1944). In this a most unusual condition, imbecility associated with pseudohypertrophic muscular dystrophy and, in some cases, neurological symptoms, was confined to males and transmitted through normal females for five generations (Figure 16).

#### OCULOCEREBRORENAL SYNDROME

This name has been given to a disease which was first recognized by Lowe, Terrey and MacLachlan (1952). They studied three male infants in whom the critical phenomenon was proteinuria. Symptoms included failure to thrive, mental retarda-



tion, evidence of rickets and cataracts with glaucoma. The primary lesion is thought to be situated in the kidney tubules. Seboen and Young (1959) reported male twins both of whom had the syndrome, and Dent and Smellie (1961) described two unrelated boys, with the condition, each of whom had a brother identically affected. The disease has the sex-linked pattern of inheritance. Female carriers of the gene can be detected by ophthalmological examination (Donnell, 1961).

#### NEPHROGENIC DIABETES INSIPIDUS

Nephrogenic diabetes insipidus is characterized by excretion of large quantities of dilute urine. There is excessive thirst and no response to antidiuretic hormone. Patients do not thrive; they suffer from constipation and attacks of fever. The maintenance of adequate hydration is essential for well-being. Some of the survivors are mentally retarded (Kirman, Black, Wilkinson and Evans, 1956).

A renal tubular defect leading to failure of water reabsorption has been thought to be the basis of the condition. A number of pedigrees have indicated a sex-linked mode of inheritance with transmission through females to males (Forssman, 1945, Williams and Henry, 1947). Affected females have been described (West and Kramer, 1955). Carter and Simpkins (1956) found, with a urine concentration test, a significant reduction in the mean specific gravity of the urine from normal mothers and maternal grandmothers of patients.

#### ANHIDROTIC ECTODERMAL DYSPLASIA

A curious rare condition, almost confined to males and usually inherited through the female line, is characterized by absence of the sweat glands (anhidrosis), peculiarities of the skin and other ectodermal tissues. The skin is smooth, hair growth is scanty, dentition is faulty and teeth may be absent altogether. Patients suffer severely in hot weather. Among the pleiotropic effects of the gene concerned, diminution of intellectual capacity to the level of feeble-mindedness has been recorded. Halperin and Curtis (1942) collected and analysed a group of published cases. In these sibships, if allowance was made for selection by at least one affected male member, one-half of the males were affected and no females, as

would be expected on the hypothesis of sex-linked inheritance

Similar conditions, not necessarily related in any way to mental defect, have been described in pedigrees which indicate autosomal dominance. Many different varieties of ectodermal dysplasia, with various modes of inheritance, were listed by Cockayne (1933). It is possible that affected females are heterozygotes for the sex-linked gene, which is, thus, incompletely recessive in the female (Levit, 1935). The possibility of autosomal inheritance with a strong tendency towards male sex limitation has not been excluded. Indeed, it is not yet clear how many clinical and genetical entities are involved.

#### HYDROCEPHALY

Though the cause of congenital hydrocephaly is not established in the majority of instances (see Chapter IX), there is good evidence that a sex-linked gene is responsible in a number of cases. Bickers and Adams (1949) reported a family in which four of a healthy mother's brothers and all her three sons had hydrocephaly and died at, or soon after, birth. None of her three sisters and two daughters was affected. At post mortem, one of the sons was found to have stenosis of the aqueduct of Sylvius. Another family, reported by Edwards, Norman and Roberts (1961), had 15 affected males in three generations, with a distribution entirely consistent with a sex-linked recessive pattern of inheritance. The propositus was a hydrocephalic stillborn child with stenosis of the aqueduct in addition to apparent absence of the corticospinal tracts. Edwards (1961) reported further families which supported the view that hydrocephaly could be sex-linked. Surviving cases had severe mental defect. Edwards suggested that sex linked hydrocephaly might account for almost 5 per cent of male hydrocephalics.

#### MISCELLANEOUS PEDIGREES

A pedigree described by Njå (1945) first showed gargoylism, previously considered to be an autosomal recessive disease, inherited very probably as a sex-linked trait. Since then many pedigrees which can be similarly interpreted have been recognized (Millman and Whittick, 1952) (see Plate V). Possibly one quarter of all cases of gargoylism fall into this group. Unless a transmitting unaffected female occurs in the family, the

genetical type remains doubtful even though the patient is male and has affected brothers. Progressive deformity of the skeleton follows the same pattern in both autosomal and sex linked conditions. So also does the enlargement of the liver and spleen. Urinary excretion of mucopolysaccharides (Dorfman and Lorincz, 1957) and the presence of inclusion bodies in lymphocytes (Mittwoch, 1959) are similar in both genetical types. The only distinctive peculiarity is the absence of corneal opacity in the sex linked variety.

Roberts (1937) investigated a pedigree of bilateral microphthalmos associated with severe mental defect. Only males were affected and the mode of transmission indicated sex-linkage. Autopsy carried out on one member of this family, who was an idiot by Whitnall and Norman (1940) revealed that, besides malformation of the eyes, the optic nerves and chiasma tracts, the lateral geniculate bodies and one cortico-visual area were imperfectly developed. A study by Sjogren and Larsson (1949) on microphthalmos and anophthalmos showed that the sex linked type was of rare occurrence. The sexes were equally affected in most families and transmission was irregular. In more than one third of all cases there is mental retardation. Unilateral instances are usually sporadic. In one male imbecile with unilateral microphthalmos, a greatly lengthened large acrocentric chromosome was demonstrated (Delhanty and Shapiro, 1962).

An apparently sex-linked type of severe mental defect was described in two brothers and their maternal uncle, by Börjeson, Forssman and Lehmann (1962). Two maternal aunts and the maternal grandmother were mildly subnormal. Besides imbecility the three male patients had hypogonadism and obesity and two were epileptic.

A pedigree described by Wolfslast (1943) contained males with mental defect, spastic diplegia, athetotic movements and nystagmus. Five males were affected and inheritance was through normal females.

Pelizaeus Merzbacher disease is a progressive demyelination of white matter which produces spastic paralysis and idiocy in the first decade of life. It is an extremely rare hereditary condition. Males, who are much more frequently and more severely affected than females, have never been observed to transmit it.

The assumption has usually been made (Gates, 1946) that the disease is sex linked with incomplete recessivity in females but a sex-influenced autosomal gene would also explain the pattern of inheritance

#### THE BIOLOGY OF SEX LIMITATION AND SEX LINKAGE

There are many conditions, in which the genetical basis is well established but which nevertheless occur more frequently or more severely in one sex rather than in the other, that is to say they show some degree of sex limitation. In many recessive abnormalities male cases predominate. Examples of such conditions are albinism, alkaptonuria, diplegia, spastic paraplegia, retinitis pigmentosa and juvenile amaurotic idiocy. There is also a predominance of male cases among low grade defectives in general and in the non specific recessive type described by Sjogren (1935). Two exceptional conditions are phenylketonuria and anencephaly though the excesses of female cases here might result from greater severity of the diseases in males, sufficient to produce early death leading to their exclusion from pedigree records.

The converse of this is found in several diseases with onset in late or middle life and probable dominant inheritance. Huntington's chorea (Bell 1934, Malzberg 1935) has an onset earlier in females than in males. The same applies to the group of diseases, with irregularly dominant transmission classed under the heading of manic depressive psychosis. The age of breakdown in females is earlier and the incidence higher than in males (Dayton, 1940).

A biological explanation of these phenomena may be sought in the differential selective advantages of modifying genes in the two sexes. Thus, as first pointed out by Levit (1935) there is only selective advantage for modifiers which delay the onset of dominant diseases in the reproductive period. Since the reproductive period lasts longer in males than in females, genetic modifiers are likely to have been favoured because they delay onset in males longer than in females (Penrose, 1942). The opposite tendency, noticed in the greater severity of recessive diseases in males than in females, is more difficult to explain. Perhaps the critical fact is the greater fertility in females than in males with equally severe defects. Genes which favour-

ably modified recessive diseases in females would have more selective advantage than those which modified the same diseases in males. This principle could apply to all types of severe defect irrespective of the mode of inheritance. The theory has often been advanced that the modifying factors which produce more male than female cases of severe subnormality are themselves sex linked genes (Sjogren 1932, 1935, Rosanoff, 1931). It has however, no support from statistical analysis (Csik and Mather, 1938). Variations in the reactions of the sexes to the presence of different abnormal genes depend chiefly upon the autosomal constitution.

## CHAPTER IX

### FOETAL MALFORMATION OF GENETICAL ORIGIN

*Incidence of Foetal Malformations—Anencephaly, Hydrocephaly and Spina Bifida—Naevoid Amentia—Clinical Picture of Mongolism—Aetiology of Mongolism—Familial Incidence of Mongolism—Karyotype in Mongolism—Multiple Origins of Mongolism—Microphthalmos Harelip, Cleft Palate and Polydactyly—Micrognathism with Associated Malformations—Miscellaneous Chromosomal Aberrations—Pathology of Chromosomal Aberrations*

#### INCIDENCE OF FOETAL MALFORMATIONS

A WIDE variety of abnormal conditions is considered under the general term of foetal malformation. These conditions are the end results of growth disorders in early developmental stages. They can affect the whole body or only parts of it. Their importance here lies in the surprisingly high proportion of such malformations that cause mental defect, often of an extremely severe degree. Some deformities, like anencephaly and mongolism, are invariably associated with mental defect and others, like club foot, spina bifida and harelip, occasionally. Nomenclature of these conditions is troublesome because several types of deformity often coexist in the same individual. Thus, spina bifida occurs with or without hydrocephaly and either of these conditions can occur with club foot. Furthermore, congenital cardiac disease frequently accompanies mongolism. The most extreme deformity present usually determines the diagnosis.

In the classical survey made by Malpas (1937) at the Liverpool Maternity Hospital, more than 1 per cent of infants born showed malformations affecting the brain and almost as many had miscellaneous defects. Table XXXVI shows the frequencies of the important types. Hydrocephaly is the most common deformity shown in this table. It was also the most common condition in the material collected by Murphy (1947) who examined the deaths and stillbirths in Philadelphia, over the

period of a year. On this basis he estimated that approximately 0·5 per cent of liveborn and 3 per cent of stillborn individuals were malformed. The incidence in the white as compared with the coloured population was as nine to five, and for parents of British origin, judging by the United States Government statistics on infant mortality, the incidence was higher than for any other group. Marked degrees of variation in the frequencies of malformations have been demonstrated by comparing the results of surveys on different populations. The combined incidence at birth of anencephaly, spina bifida and hydrocephaly in Dublin was found to be 1·27 per cent by Coffey and Jessop (1955); in Birmingham the corresponding figure was 0·57 per cent (Record and McKeown, 1949) and in Zurich it was 0·23 per cent (Ehrat, 1948).

TABLE XXXVI

FOETAL MALFORMATIONS IN A SERIES OF 13,964 BIRTHS,  
after Malpas (1937)

Abnormality	Number of Cases	Percentage Incidence
<b>Cerebral</b>		
Anencephaly and related conditions	44	0 31
Spina bifida	39	0 28
Hydrocephaly	58	0 42
Mongolism	18	0 13
<b>Total</b>	<b>159</b>	<b>1 14</b>
<b>Miscellaneous</b>		
Club foot	23	0 17
Malformed hands	16	0 11
Absence of radius	2	0 01
Harelip and cleft palate	17	0 12
Hypospadias	16	0 11
Congenital cardiac disease	10	0 07
Gastroschisis	5	0 04
Other	38	0 27
<b>Total</b>	<b>127</b>	<b>0 91</b>

It is interesting to note that, if intelligence could be measured at birth in every child, the incidence of mental defect would be found to be much higher than that observed at school age. About 1 per cent would be idiots. On the other hand, the

normal variability would be much greater than is observed in later life, because prematurity, postmaturity and different individual rates of development would complicate the picture. This serves to emphasize that when the incidence of mental defect in a given population is stated, the age group must also be specified. By the age of 10 years the incidence of idiocy has dropped to 0.06 per cent because of the high mortality rate of low-grade defectives.

The study of causation of these foetal malformations presents one of the most fascinating problems in medicine (Haldane, 1938a). One certainty is that the defects must originate at an early stage in embryonic development. The most significant period, from the point of view of these malformations, precedes the 12th week of pregnancy. Any environmental cause to be sought must act before that time and the crucial period may be as early as six to eight weeks. At certain critical stages in development several widely different types of disturbance, genetical or environmental, may lead to similar results, in the same way that, in later life, there may be many different causes for the same reactive symptom like a fever or convulsion. Experiments in animal breeding have been useful in suggesting genetical causes. Snell and Picken (1935) found that anencephaly in mice might follow from the presence of too much chromatin or too little. There are other genetical causes for similar conditions in animals. One kind of hydrocephaly in the mouse is a single gene recessive trait (Gruneberg, 1943), another kind is due to a different gene, also recessive. A monstrosity found in some stocks of guinea pigs, characterized by defect of the lower jaw in mild instances and complete absence of the head in the most severe instances, is known as otocephaly. Wright (1934) has shown that it is partly determined by genes. Some unknown factors, connected with the maternal environment, also contribute to the causation. This condition exemplifies the way in which the circumstances existing before conception combine with those existing during individual development to cause foetal abnormality in a mammal. Thus, with human malformations, in some cases genetical causes, in others environmental causes are to be suspected. In yet others, a combination of causes is to be blamed. Consequently, human data on foetal malformation must be surveyed simultaneously from the



points of view both of genetics and of the study of maternal environment. The effects of external influences in producing malformation are described in Chapter X.

#### ANENCEPHALY, HYDROCEPHALY AND SPINA BIFIDA

It is convenient to group together all the gross malformations of the nervous system, partly because they have certain common features in their natural history and partly because such malformations are often associated with one another in the same individual. All these defects must originate very early in embryonic life, probably within the first eight weeks, their causation therefore is limited to events occurring not later than the very early prenatal period.

Anencephaly is not compatible with mental functioning or even with independent life for more than a day or two. In one reported instance, however, the subject lived for several months. The brain is replaced by amorphous vascular tissue and the vault of the skull is absent. Hydrocephalics are not so completely disabled though most congenital cases show marked mental defect. In some of these, the child may live many years although the head can continue to enlarge, occasionally to a prodigious extent. When this occurs the skull becomes so extremely thin that membranous lacunae appear and multiple Wormian bones develop in the sutures. The ventricles are enormously dilated and the cortex is stretched and deformed out of all recognition. As with some other types of neurological defect, in spite of great disability, due to blindness or paralysis, the subject's intelligence may be greater than the casual observer would be led to suppose. Both anencephaly and hydrocephaly are not infrequently accompanied by some degree of spina bifida. There are also intermediate conditions, such as the Arnold Chiari malformation in which cerebellar tissue protrudes through the foramen magnum, and milder defects of the neural tube producing meningocele only. Spina bifida, by itself, is not necessarily associated with mental defect. Very mild cases of spina bifida occulta are compatible with quite normal development and are believed by some authorities to be common in the normal population.

Anencephaly is such a striking abnormality that its occurrence is usually recorded even though other malformations may be

listed inadequately. In different parts of the world the incidence varies greatly. The highest known frequency at birth is found in Ireland and this exceeds 0.5 per cent. The usual level in continental Europe is about 0.1 per cent. In Chinese populations the corresponding figure is 0.05 per cent and among native Africans it is 0.02 per cent. In mixed immigrant populations, the incidence for each group agrees with that found in the country from which its members originated (Penrose, 1957, Searle, 1958). This fact points to a genetical determination of the incidence variations. Environmental determination is indicated by changes in seasonal incidence (McKeown and Record, 1951).

Familial investigation of nervous system malformations usually leads to a negative result in the sense that second cases of the same kind are comparatively rarely discovered in near relatives. Sometimes, however, the same abnormality is repeated in more than one sib. Familial anencephaly was reported by Schade (1939), for example. Murphy (1936), moreover, drew attention to the fact that, though the same abnormality is sometimes repeated in a sibship, at least as frequently different abnormalities occur in two or more sibs. As shown by Polman (1951) anencephaly, hydrocephaly and spina bifida can occur in closely related sibships. With common conditions, that is, conditions with an incidence of the order of 1 per cent, it is not always easy to exclude chance coincidence, and careful study of unselected samples is required. The available evidence suggests that familial incidence in these malformations is slight but significant. If one child with anencephaly or spina bifida is born, the chance that the same pair of parents will have another child with severe neurological malformation lies between 3 and 10 per cent.

Reservations have to be made in forming an estimate in any given sibship because, as has been shown in Table XXV, p. 117, there is a marked tendency for risks of malformed offspring to increase in the later maternal age groups. The same applies to statistics of stillbirths generally (see Table XXXVII), and this is not surprising, for foetal malformation is an important cause of stillbirth and also of neonatal mortality (Holland and Lane-Clayton, 1926). Birth rank by itself has apparently much less effect than maternal age, though there seems to be

an increased risk of malformation for the first born. Possibly there is, also, increased risk for very young mothers as well as for those nearing the end of the child-bearing period.

TABLE XXXVII

INCIDENCE OF STILLBIRTHS ACCORDING TO MATERNAL AGE

Maternal Age	Maternities	Stillbirths	Incidence of Stillbirths
15-19	25,849	558	0.022
20-24	177,191	3,774	0.021
25-29	184,352	4,279	0.023
30-34	165,819	4,776	0.029
35-39	103,426	4,030	0.039
40-44	31,974	1,745	0.055
45-49	2,323	171	0.074
All Ages	690,934	19,333	0.028

From *Statistical Review of England and Wales for the Year 1945* (New Annual Series, No. 25), Tables—Part II, Civil, p. 113

From a study of the facts presented here and in previous chapters it is evident that no single cause can be responsible for all cases of severe nervous system malformation or even for cases of any one type. Anencephaly has sometimes recessive determination but in most instances its origin is unknown. Congenital hydrocephaly is occasionally a sex-linked defect; it can be an autosomal recessive trait but, again, its cause is usually not ascertainable. Spina bifida also behaves as a recessive condition in a considerable proportion of cases. Many other causes have been suggested. Among these are genetical factors affecting the constitution of the mother, infectious diseases and nutritional influences. Chromosomal investigations on anencephalics have not revealed any characteristic abnormalities (Harnden, 1961).

Another explanation, which needs careful study, is that mentioned by Kemp (1944), namely, that fresh gene mutations account for many cases. Deformities of the nervous system tend to be lethal; every time such a child is born and dies, genes which are causal will be lost. It can be argued that, to conserve equilibrium, the genes for anencephaly must be continually replaced by new mutation. If so, the mutation rate

must be high. However, inferences about mutation rates in diseases whose incidence is related to increased maternal age or parity need to be very guarded.

#### NAEVOID AMENTIA

Localized angiomas are among the commonest kinds of congenital malformations and their causes are largely unknown. One special type, significant in relation to mental deficiency, and formerly termed naevoid amentia, implies the combination of a meningeal and facial angioma. The condition is also known as Sturge-Weber or, more correctly as Weber (1947) modestly pointed out, Sturge Kalischer disease. The naevoid condition in the skin is predominantly unilateral and calcification around the intracranial vessels on the affected side is demonstrable by X-ray. Hemiplegia is often an accompaniment and epilepsy an almost invariable symptom. Mental impairment is usually of mild degree and it is not closely correlated with the extent of the lesion. The main features of the condition are shown in Plates VIa and VIb. Familial recurrence of this syndrome has not been recorded and there is no indication that parental age or birth order is aetiologically significant. Mutation in somatic cells is a theoretical possibility (cf p 221).

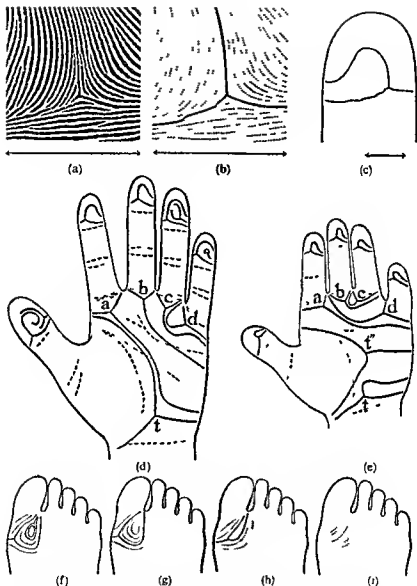
Sturge-Weber-Kalischer disease must be distinguished from traits involving the presence of multiple naevi and not concerned with mental subnormalities, such as Osler-Rendu disease, which is described as dominant in some families. The same applies to cystic naevus of the cerebellum, retina and other structures, known as the syndrome of von Hippel and Lindau, which is also dominant, though it is usually not found in more than one member of a family (Craig, Wagner and Kernohan, 1941).

#### CLINICAL PICTURE OF MONGOLISM

A central position in the study of mental deficiency is occupied by the problem of mongolism. Some 10 per cent of all hospital cases belong to this class. In early times these people were probably confused with cretins and were thought to be caused by parental tuberculosis. Langdon Down, in 1866, first recognized the condition as a separate clinical entity. He described these patients as mongolian or mongoloid because

of their superficial resemblance to normal oriental peoples and particularly to the Kalmucks. The hypothesis, added later by Crookshank (1931), that these patients were derived from Mongolian ancestors and, further, that they represented an atavistic return towards the orang utan, has no scientific validity. The anomaly has been reported in almost all parts of the world, among the children of American negroes (Thompson, 1939) and Chinese as well as in Japan, Africa and India. It is probably most frequent, however, in populations of European origin. Sometimes the term mongolism is replaced by an equivalent such as Down's disease or the Langdon Down anomaly to avoid racial connotation.

The malformation affects, in some degree, almost every part of the body (see Plate VII). Many of the characters by which mongolism is recognized are also found less frequently in other types of defectives and even in normal subjects. Of the external peculiarities, the most noticeable are dwarfed stature, a small round head and dysplastic face. The retardation of growth has been studied by Benda (1947), who considered that the mongol infant is of normal length at birth, that it deviates progressively from the normal as it grows older and ultimately reaches, on the average, a stature equivalent to that of a normal child of 10 years. Actually the mean birth weight is below normal by nearly 1 lb. Adult body weight is correspondingly reduced. The head is notable for its small dimensions. The anterior fontanelle is late in closing (Roche and Sunderland, 1960). At birth a third fontanelle is found at the vertex. The anteroposterior diameter is greatly diminished and the cephalic index is high (see Table XXXI). The hair is usually straight and sparse and the skin is dry. Indeed, dry rough skin was noted by Seguin as a very characteristic feature of patients whom he called furfuraceous cretins in 1863 and who were probably of the same type called mongols by Langdon Down. The face, which sometimes suggests an oriental configuration, is notable for its flatness and hypoplastic nature, with a short and squat nose, small rounded ears with prominent antihelix and oblique palpebral fissures. Epicanthic folds of skin make the intraocular distance seem unusually wide though it is actually diminished (Kerwood, Lang-Brown and Penrose, 1954). Cataract, myopia, strabismus and iris with peripheral white speckling are charac-



**Figure 17 —Dermatoglyphic features in mongolism**

- (a) Part of a finger print (magnified)
- (b) Triradius and corresponding main lines formed by dermal ridges (magnified)
- (c) Diagram of whole finger tip showing same triradius and main line loop pattern
- (d) Right hand of normal adult male showing triradii, main lines and flexion creases
- (e) Right hand of male mongol, note ulnar loops on fingers, small loop between b and c and distal triradius t
- (f) Hallucal area showing normal type of whorl
- (g) Hallucal area showing large digital loop
- (h) Hallucal area with narrow digital loop (sometimes found in mongolism)
- (i) Hallucal area with open field ridge pattern (very characteristic of mongolism)

teristic of the eyes themselves (Brushfield, 1924, Lowe, 1949); blepharitis and conjunctivitis often develop. The mouth is notable for a protruding chin and lower lip, thickened buccal mucosa and a fissured tongue with enlarged papillae. Development of the teeth is commonly retarded and irregular. Unusual susceptibility of mucous membranes to infection is indicated by the prevalence of nasal and respiratory catarrh. Since antibody formation in mongolism is normal (Donner, 1954) liability to infection may depend upon abnormal tissue morphology. The mortality rate at all ages is very high, probably greater in females than in males, and the expectation of life at birth is about 12 years. One female living to the age of 83 has been reported (Simons and Speijer, 1937).

The limbs are stumpy, like the trunk. Pelvic anomalies were noted by Caffey and Ross (1956). Joint ligaments are lax and mongol children sit comfortably in the tailor-wise position. The hands and feet are broad and clumsy, and webbing (zygodactyly) of fingers and toes is not uncommon. The little finger tends to be very short and to curve inward. Of particular interest are the configurations of the flexion creases and of the dermal ridges on the palms and soles. A single transverse crease often runs across the palm of the hand, two creases on the little finger may be replaced by one only and a marked cleft occurs between first and second toes. The dermal ridges, first studied by Cummins (1936), have a more transverse arrangement than is usual in normal hands. This is shown especially in the horizontal path of the main line from triradius *a* and the position of the axial triradius *t*, as demonstrated in Figure 17. Hypothenar patterns are common in mongolism but thenar patterns are very rare. An ulnar loop is the characteristic fingerprint pattern (Turpin and Caspar-Fonmarty, 1945, Holt, 1950) but radial loops occur on digits IV and V. Normally there is often a whorl on the hallucal area on the sole; in mongolism patterns in this region are rare (Ford Walker, 1957).

Other abnormalities include umbilical hernia and small genital organs; greatly reduced sperm counts have been noted (Stearns, Droulard and Sahhar, 1960). On the neurological side, the absence of signs of organic disease is remarkable. Epilepsy is no more common than among members of the general population.

The mental grade varies from idiocy to an upper limit at about the 7-year level, as judged by the Binet tests. Institutional cases have a mean IQ between 20 and 25 points, but those living at home may be of higher grade, and can be useful in domestic occupations under supervision. The highest mental age reached is hardly ever above 7 years so that, in adults, the IQ is below 50. Typical mongols have cheerful and friendly personalities. Their capacities for imitation and their memories for people, for music and for complex situations may be found to range far beyond their other abilities. They are incapable of abstract reasoning. They cannot do arithmetic although they may sometimes be able to read and write.

The underlying pathology is still obscure in spite of much intensive investigation. The brain shows no constant morphological peculiarities other than a tendency towards embryonic convolucional patterns and a disproportionately small cerebellum and brain stem (Davidoff, 1928). Histologically, paucity and irregular disposition of ganglion cells in the third cortical layer and retarded development of the spinal cord have been demonstrated (Benda, 1940). Changes in the pituitary gland, thyroid gland and suprarenals have frequently been reported, but they are not consistently present. However, Benda (1947) considers that the pituitary is always sufficiently abnormal to warrant the conclusion that this disturbance is primary. Among the abnormalities found in other organs, those in the heart, noted by Garrod (1894), are most significant medically. Typically the heart and arteries are poorly developed and there are septal defects (Berg, Crome and France, 1960). Intestinal atresia is not infrequent.

Functional biochemical tests have not yielded very characteristic results. Bixby (1941) concluded that the quantitative levels of fibrin, albumin, globulin, total protein and cholesterol in the blood were normal. Tests for carbohydrate metabolism give normal results (Bixby and Benda, 1942), as also do tests for mineral metabolism and analyses of urinary constituents. The basal metabolic rate is usually low. Decreased quantities of blood calcium were found by Stern and Lewis (1958a) and diminished urinary excretion of tryptophane metabolites was reported by Jérôme, Lejeune and Turpin (1960). Himwich and Fazekas (1940) measured the amount of oxygen utilized by the



brain. They concluded that, in mongolism as in phenylketonuria, there is a real diminution of cerebral metabolism.

Systematic blood typing of mongols and of their close relatives has revealed no appreciable divergences from general population antigen frequencies. The amount of antigenic incompatibility between mother and child, however, is reduced and this finding is perhaps connected with the late birth ranks of the patients. Incomplete segmentation of polymorphonuclear leucocytes, studied by Turpin and Bernyer (1947), Shapiro (1949) and Mittwoch (1961) is a consistent anomaly unconnected with reaction to infectious disease. For infant mongols the risk of lymphatic leukaemia is increased twenty-fold (Stewart, 1961).

Since no single clinical sign of mongolism is specific, the diagnosis has to be based upon accumulating points in its favour either deliberately or unwittingly. Signs which are ascertainable at birth are diminished head length, presence of a third fontanelle, epicanthic folds, iris specks, typical dermal creases and ridges, indications of diminished stature, poor circulation and general debility. In children and adults the mental state is very characteristic. Nevertheless, occasionally diagnosis is extremely difficult and judgment must be reserved until the results of cytological examinations have been obtained.

#### AETIOLOGY OF MONGOLISM

In consequence of the high mortality rate of mongols at all ages, especially during the first year of life, the incidence of the condition in the population diminishes in successive age groups. At birth surveys have indicated that the incidence in populations of European origin is of the order of one in 700. The results of several investigations are given in Table XXXVII. These estimates contrast with the survey made by Doxiades and Portius (1938) who ascertained 58 surviving mongol defectives in a total general population of all ages of 415,431 in Germany, implying an incidence of one in 7000.

The incidence also varies with maternal age in a remarkable manner, as can be seen from the statistics given in Table XXXIX and Figure 18. The numbers of cases in each maternal age group are taken from Beall and Stanton (1945). The control population is calculated on the basis of the distribution

but it can be shown that, when the influence of maternal age is eliminated, any residual effect dependent upon order of birth by itself is insignificant (Penrose, 1934b). In spite of this, some surveys have indicated that the risk of mongolism is increased for first born children (Smith and Record, 1955). The interval between the birth of the preceding child and that of the mongol has often been noticed to be longer than usual for sibs. Murphy (1947) considered that the births of malformed infants of all kinds, including mongols, tended to be preceded by a period of diminished fecundity, expressed either by a long non pregnant interval or by a series of miscarriages. Conversely, Fantham (1925) attributed mongolism to too frequent pregnancies.

TABLE XL  
SIBS OF PATIENTS IN COLCHESTER SURVEY (1938)

Diagnosis	Mongol sm	Other Types of Defect
Number of patients	63	1 217
Number of sibs of patients	366*	6 263†
Number of sibs per patient		
Normal intelligence		
Superior	0 05	0 05
Average	4 02	2 79
Dull	0 11	0 40
Unascertained	0 02	0 18
Mentally defective		
Feeble minded	0 03	0 22
Imbecile	0 06	0 09
Idiot	0 03	0 04
Miscarriages or stillbirths	0 54	0 72
Died in early infancy	0 95	0 65
Total	5 81	5 14

\* Among these were 4 cases of mongolism

† Among these were 7 cases of mongolism

Facts about fertility of the mothers of mongols are relevant to the question of causation. Jenkins (1933) believed that sibships containing mongol children had fewer members than average sibships. In the Colchester Survey, however, sibships, selected by the presence of at least one mongol, were larger than those selected by the presence of at least one defective of other type. There were also somewhat more deaths in early infancy in the mongol sibships though slightly fewer mis-

carriages were recorded, as shown in Table XL. The incidence of defectives in the mongol sibships was very low, only eight in 366 sibs and four of these were probably also mongols. Maternal health during pregnancy has been carefully studied by many observers with a view to elucidating the cause of mongolism, without leading to positive results (Oster, 1953). Premature delivery or threatened abortion might be the effect, but could not be the cause, of a malformed foetus. Maternal endocrine disturbance such as dysthyroidism (Myers, 1938) has been often suspected, but the evidence is not convincing. There seems to be no definite evidence of any maternal illness or disability characteristic of pregnancies terminating in the birth of a mongol child.

#### FAMILIAL INCIDENCE OF MONGOLISM

Familial mongolism has been described in medical literature, and indeed it is not so uncommon as Goddard (1914) supposed. Sibships containing four cases were reported by Babonneix and Villette (1916), by Péhu and Gate (1937) and by Turpin and Lejeune (1953), and instances of three cases in one sibship have been reported, long ago, by Fantham (1925) and by van der Scheer (1919). Pairs of affected sibs occur about once for every 100 single cases collected at random. Examples of uncle and niece, aunt and nephew, as well as first-cousin pairs can be found when large enough surveys are attempted, as well as pairs of cases interrelated in other ways (Doxiades and Portius, 1938, Lahdensuu, 1937 and Hanhart, 1944). Analysis of familial instances reveals that transmission through the mother predominates over that through the father. When a maternal relative is affected, moreover, the maternal age at the birth of the mongol is younger (Penrose 1951). The most striking examples of maternal transmission are those in which the mother herself is a mongol. No example of a mongol father is known but 13 offspring of female mongol patients have been recorded as shown in Table XLI. The maternal ages at the births of these patients are distributed characteristically with a mean value of about 36 years. In contrast, the ages of the mongol mothers at the births of their own affected children were much younger. Five of the 11 live born offspring were certainly mongols and two others were mentally subnormal.

TABLE XLI

OFFSPRING OF MONGOL FEMALE PATIENTS

Descript on of child	Age of Mongol Patient at the birth of her child	Maternal Age at b rth of mongol patient	Source
Normal female	25	?	Sawyer (1949)
Mongol male	30	42	Lelong <i>et al</i> (1949)
Mongol female	19	30	Rehn and Thomas (1957)
Retarded male	30	42	Forsmann and Thyrell (1957)
Idiot female	29	39	Schlaug (1958)
Mongol female	21	44	Hanhart (1960)
Mongol male	23	44	Hanhart (1960)
Normal male	?	?	Levan and Hsu (1960)
Normal male	22	22	Mullins Estrada and Gready (1960)
Stillborn male twins	14	?	Thul neand Priest (1961)
Normal male	21	40	Thompson (1961)
Stillborn female	20	22	Thompson (1961)
Mongol male	22	22	Thompson (1961)

Further evidence of genetical causation of mongolism has come from the study of twins. In most instances the twin of a mongol child is normal and the pair are then dizygotic. A few examples are known of dizygotic pairs with both twins affected (Keay, 1958). Monozygotic pairs have been found equally affected as a rule.

The sex ratio in mongolism is as four to three in favour of males (Hug, 1951). There is however, no suggestion of sex-linked inheritance. Parental consanguinity is rarely found and ordinary autosomal recessive inheritance is not indicated. In exceptional instances a gene might increase the risk of mongol children for homozygous normal mothers (see p 217). A kind of irregularly dominant influence not following any Mendelian pattern is seen in some families and this has been interpreted as evidence of the transmission of chromosomal aberration (Penrose, 1939f).

Maternal age is a factor of major importance in the aetiology of three quarters of the cases and the great majority of these have no affected close relatives. When there is clear evidence of hereditary transmission through the mother, normal or affected, the effect of maternal age is demonstrably much weaker. Indeed the bimodal tendency of the distribution curve by maternal age

could be explained if about one-quarter of all mongols belonged to a category in which this age factor was not aetiologically significant.

#### KARYOTYPE IN MONGOLISM

It has been suspected for a long time that some chromosomal aberration might be implicated in the pathology of mongolism. Waardenburg (1932) suggested non-disjunction as the type of aberration most likely to be responsible. Investigation of the chromosomes of a mongol during spermatogenesis (Mittwoch, 1952) led to the conclusion that, in diakinesis, there were 24 chromosomal masses; this number was not considered exceptional but Ford and Hamerton (1956) demonstrated that the normal number was 23. Somatic chromosomes were studied in fibroblast cultures by Lejeune, Gautier and Turpin (1959) with improved technique and a specific aberration was identified, namely the presence of a small extra chromosome, probably a No. 21. It is generally accepted that this aberration (illustrated in Plate VIII) is usually the result of non-disjunction during gametogenesis; the association with maternal age and maternal transmission indicates the ovary rather than the testis as the place of origin of this standard mongol trisomic karyotype.

A number of variant karyotypes have been described in mongolism (Figure 19). First there is the association with Klinefelter's syndrome (Ford, Jones, Miller, Mittwoch, Penrose, Ridler and Sapiro, 1959) in which the patient showed simultaneously the characteristics of two anomalies. Such individuals might be expected to occur only with the combined frequency of both conditions, that is  $1/700 \times 1/800$ , or one in half a million births, unless factors exist which produce a general non-disjunction tendency.

Secondly, there is a very important group of variants in each of which translocation of the No. 21 chromosome is involved. A fracture is assumed to have taken place at or near the centromeres of two chromosomes and the wrong pair of ends has rejoined. This process is called centric fusion by White (1954). In the commonest of these variants the greater part of a No. 21 is fused with a chromosome of the 13 to 15 group, probably No. 15. The chromosomes in question are shown diagrammatically in Figure 19(d) and (h).

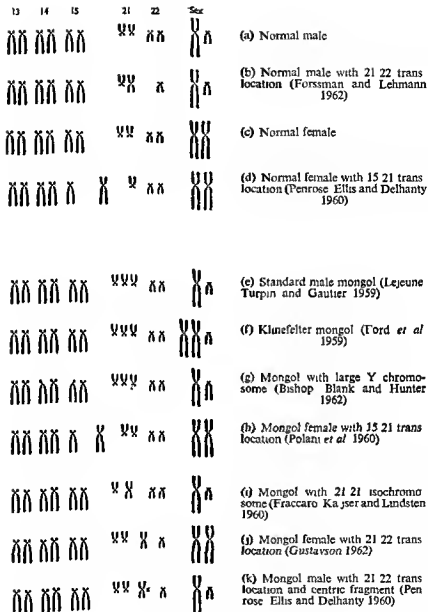


Figure 19 —Human karyotypes showing acrocentric and sex chromosomes only

A mongol whose cells contain such a fusion has only 46 chromosomes (Polani, Briggs, Ford, Clarke and Berg, 1960) because the minute chromosome formed by junction of the two short arms of 21 and 15 seems almost invariably to disappear after several generations of cells. Clinically the result of having a long arm of No 21 chromosome extra is the same whether it is attached to another chromosome or whether it is isolated as in the standard karyotype. The most remarkable feature of this kind of mongolism is that in most instances the mother is found to carry the same translocation and to have only 45 chromosomes although she is perfectly normal. However, such a woman is liable to have mongol offspring irrespective of her age because the presence of a translocation interferes with regular gametogenesis. Thus the two homologous chromosome pairs 15, 15 and 21, 21 in a normal person are distributed in each mature gamete regularly as 15, 21. If there is 15 21 fusion present, there are several different arrangements possible in the mature ova. The oocyte containing the three chromosomes 15, 15 21, 21 can produce mature balanced gametes with two normal chromosomes 15, 21 or with one fused chromosome 15 21. Either of these will lead to normal offspring when fertilized by a sperm with chromosomes 15, 21. But unbalanced ova can also be produced, such as one with chromosomes 15 21, 21, which will lead to a mongol when fertilized, and another with only 15 which will probably not survive. In spite of these risks a 15 21 chromosome can descend through many generations of normals unsuspected until a mongol occurs in the family, although females who carry it are predisposed to produce mongols, the same does not appear to hold for all the males who carry it.

Another type of translocation found in mongolism concerns two chromosomes of the 21, 22 group. It is, again, a centric fusion but there is uncertainty whether two No 21 chromosomes are involved as an isochromosome or whether the long arms of a 21 and a 22 are joined. As in the 15 21 type of translocation, a supplementary minute chromosome has occasionally been detected (Penrose, Ellis and Delhanty, 1960). There seems to be no appreciable difference clinically from the standard trisomic type but there are some aetiological peculiarities. Familial instances have been described and, in such cases,

inheritance can be through the father. In the family described by Forssman and Lehmann (1962), the normal father had only 45 chromosomes because he possessed a 21:22 type fusion and in the first case described (Fraccaro, Kaijser and Lindsten, 1960) the father had in some of his cells an extra chromosome of this same fused type. Surprisingly there seems to be a significant increase in paternal age for this group of patients (Penrose, 1962) but, since they only represent about 1 per cent of all mongols, this effect is smothered if data from every type are pooled (see also p. 221).

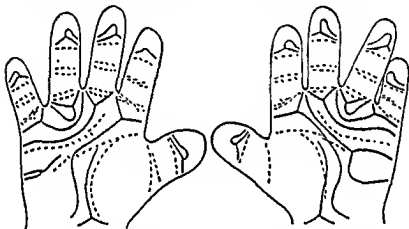


Figure 20.—Dermal ridge main lines on palms of female mosaic mongol (Clarke, Edwards and Smallpeice, 1961.)

The radial loops on digits IV and hypothenar patterns suggest mongolism but the loops between c and d do not (see Figure 17).

A third group of aberrations found in mongolism is concerned with mosaicism, that is to say, more than one karyotype is present in the same individual. The most usual variation is that some of the patient's cells are trisomic although a substantial number are normal (Clarke, Edwards and Smallpeice, 1961). If a large majority are normal the individual may be expected to develop fairly normally in spite of showing some signs of mongolism (see Figure 20). Such a person might have a considerable risk of producing mongol offspring. One of the consequences of establishing the existence of mongol mosaicism



has been that it may explain several obscure observations. The existence of clinically intermediate, partial mongols or *formes frustes* has always been difficult to explain, moreover resemblance between the patient and unaffected close relatives, especially the mother, in respect to mongol signs or micro-symptoms has often been observed (Penrose, 1954). Mosaicism in normal relatives might be an explanation of many of these phenomena.

#### MULTIPLE ORIGINS OF MONGOLISM

It is clear from the facts which have been presented that there is a large variety of circumstances, each of which can lead to mongolism as the end result. In one class (A) we can include all those cases in which maternal age is not a significant factor. In all of them there is some degree of familial tendency. They amount to about 25 per cent of the total number. The group can be further subdivided and each division separately considered.

- A (i) The mother herself is a mongol. In this exceedingly rare class, the cause of mongolism in the child is inevitable or secondary non-disjunction leading to standard trisomy.
- A (ii) A parent, usually the mother, carries a fusion of the type 15 21 in some or all of her cells. This group may comprise nearly 2 per cent of all mongols.
- A (iii) A parent, usually the father, carries fusion of the type 21 22 in some or all of his cells. This group may comprise nearly 1 per cent of all mongols.
- A (iv) The mother or possibly the father is a gonadal mosaic e.g. type (i), (ii) or (iii). If this is so more than one sib may be affected and some characteristic micro-symptoms may occur in the parent.
- A (v) The mother or father may carry a gene which tends to produce non-disjunction. In such circumstances more than one type of trisomy may occur in the offspring.
- A (vi) Miscellaneous, as yet unidentified, circumstances such as genes producing mitotic non-disjunction in the somatic cells of the person who carries them.

In class B, which comprises three quarters of all mongols, a

process very closely related to changes concomitant with ageing of the mother causes non disjunction and consequent trisomy of No 21. There is a curious affinity of the satellited chromosomes, Nos 13 to 15 and Nos 21 to 22, for one another which is observable during mitosis (Harnden, 1961). All of them seem to take some part in nucleolus formation and, for this reason, mutual aberration between them is not unexpected because of delayed separation in the first meiotic division of gametogenesis. Nevertheless, the actual stimulus to non-disjunction produced by maternal ageing is unknown. In plants, dehydration causes abnormal cell division and in mammals hormonal dysfunction and the accumulation of mutagenic agents have been suspected. According to some observers (Pleydell, 1957) environmental influences such as infections and climate may affect the risks of mongolism also.

#### MICROPHTHALMOS, HARELIP,

##### CLEFT PALATE AND POLYDACTYLY

A syndrome of malformations, in which the most obvious features include bilateral harelip, cleft palate, microphthalmos or anophthalmos, polydactyly and cardiac defects, has been often observed in the newborn. In those children who survive long enough for the mental state to be observed, retardation is always present. The incidence of the anomaly is of the order of one in 3000, and it was formerly considered no more than an inexplicable curiosity. Patau, Smith, Therman, Inhorn and Wagner (1960), however, described 47 chromosomes in such a case and the extra one was clearly a member of the 13 to 15 group, possibly trisomy for No 13. Since that time all children with these characteristic features whose karyotypes have been studied have shown a similar chromosomal aberration (see Figure 21).

Besides the obvious deformities noticeable in these infants, examination of the palmar dermal ridges shows a very characteristic pattern. The triradius *t* is even in a higher, more distal, position than in mongolism and patterns on the thenar aspect, very rare in mongolism, are prominent. Since infants with this syndrome are unlikely to survive for many months, the assessment of their mental development is difficult but the fact that cerebral malformation can be an accompaniment suggests

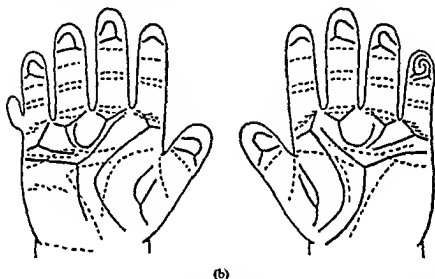


Figure 21.—Female case of trisomy 13 (14 or 15) (Ellis and Marwood 1961).

(a) Karyotype

(b) Dermal ridge main lines on palms

The distal transverse  $t''$  suggests mongolism but the thenar patterns and polydactyly do not (see Figure 17)

that in some cases the defect would be severe.

The incidence of the condition, as in mongolism, is influenced by maternal age and is greater for older than for younger mothers. Some cases, again like mongols, are probably the result of reciprocal translocation or fusion between chromosomes which are members of the 13 to 15 group. Families have been described in which such a fused chromosome has been transmitted for three generations of normal people (Walker and Harris, 1962). It is noteworthy that here, as in mongolism,

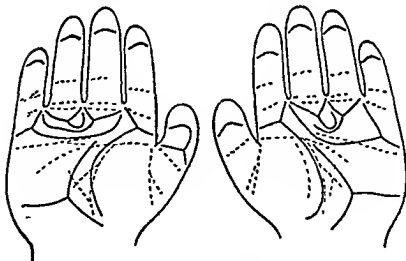
the translocations and non-disjunctions responsible for the condition concern one of the satellited chromosomes

#### MICROGNATHISM WITH ASSOCIATED MALFORMATIONS

A curious syndrome, which includes severe mental defect as a feature, seems to have been clearly recognized as an entity only after chromosomal investigations became technically possible. The first case, described by Edwards, Harnden, Cameron, Wolff and Cross (1960), was a female infant with



(a)



(b)

Figure 22 — Male case of trisomy 17 (or 18)

(a) Karyotype

(b) Dermal ridge main lines on palms

Note arches on 9 out of 10 digits and absence of distal interphalangeal flexion creases

a receding chin, low set ears, webbed neck, syndactyly of the toes, malformed chest and cardiac lesion. The karyotype of connective tissue revealed an extra chromosome believed to be a No. 17. Many instances of apparently the same abnormality have been observed since then and it is undecided whether the extra chromosome is a No. 17 or a No. 18. Few children with this syndrome survive long enough for mental level to be accurately assessed. An interesting variant is the case reported by Uchida and Bowman (1961) which was complicated by X trisomy and had a total of 48 chromosomes. Association with mongolism has also been reported (Gagnon *et al.*, 1961).

The aetiology has not been very fully investigated but it is evident that maternal age in these cases is significantly increased above the average (Smith, Patau and Therman, 1961). In other respects these infants in no way resemble mongols (see Figure 22). The palmar dermal ridge main lines are not transverse and the position of the triradius  $t$  is normal. Moreover the finger tip patterns are usually all arches. The fingers are held in a flexed position with extension of the terminal phalanges and the most distal flexion creases are absent.

#### MISCELLANEOUS CHROMOSOMAL ABERRATIONS

From time to time an extra chromosome resembling No. 21 has been found in cells cultured from mentally subnormal patients who are clearly not mongols on clinical tests. The tendency then is to assume that the aberrant chromosome is a No. 22. This situation occurred in a patient who had classical features of the Sturge-Weber-Kalischer syndrome (Hayward and Bower, 1960). Later investigation of the karyotypes of other patients with Sturge-Weber disease did not show any similar extra chromosome.

A special problem arises each time a previously unrecognized abnormal karyotype is discovered in the cells of a patient with a recognized disease. It is uncertain whether the cytological abnormality is connected with the disease or whether it is an incidental accompaniment. For example, in two cases of Marfan's syndrome, Tjio, Puck and Robinson (1960) observed very prominent satellites on certain autosomes. In cases of Marfan's syndrome tested by other investigators the same peculiarity has not been observed. Moreover, enlarged satellites

demonstrable on chromosomes in perfectly normal individuals and transmissible from one generation to the next, have been found in parents of anencephalics (Ellis and Penrose, 1961) and of mongols (Hirschhorn, Cooper, Sklarin, Rendon and Meyer, 1962) In some instances an extra chromosome is present which is itself clearly abnormal and with an origin difficult to trace like that, which was probably a No 22 with satellites at both ends, found in one case of epileptic sub-normality (Ellis, Marshall and Penrose, 1962)

Some of the most convincing examples of association between mental defect and chromosomal aberration have been the offspring of normal parents who carry balanced translocations different from those responsible for some mongols Edwards, Fraccaro, Davies and Young (1962) have described two defective sibs in one family and a single defective child in another, in both of these families the father carried a balanced reciprocal translocation involving large autosomes The defective offspring carried extra amounts of some chromosomes and were effectively trisomic for these portions though they were monosomic for other portions The patients were in every case obviously abnormal with many dysplastic features but quite unlike mongols One great value of cases of this sort is that, ultimately, investigation of their hereditary traits, blood typing, serum chemistry and so on, will give clues to the position of genes upon the autosomes

Aberrations of so many different kinds have been described in unconnected examples of mentally defective patients that orderly grouping of the material is not yet practicable In one case there is apparently a large deletion (Book, Gustavson and Santesson, 1961), in another case a large duplication (Delhanty and Shapiro, 1962) of a different chromosome In the first, a girl aged 4 years, No 16 was shortened and the child was like a mongol but only superficially, in the second a boy, aged 3, had unilateral microphthalmia and a lengthened No 13 These exceedingly rare, and perhaps unique, conditions will become important when they are grouped with others in which the same chromosome is involved in another way

One rather different kind of problem is posed by the remarkable child described by Book and Santesson (1960) nearly half of whose somatic cells were triploid with 69 chromosomes

although the other cells were normal. This patient, a boy aged 1 year, had severe mental retardation; micrognathia and syndactylism were physical accompaniments. It is difficult to explain how this mosaicism can have arisen unless two separately fertilized ova became integrated in the same individual. Triploid cultures showing the same karyotype in all cells (see Figure 23) have been obtained from foetal remnants derived



Figure 23.—Karyotype of triploid male foetus.

from spontaneous abortions (Penrose and Delhanty, 1961). It can then be assumed, in such a case, that a normal sperm with 23 chromosomes fertilized an unreduced ovum, that is to say one in which the second meiotic division failed to take place so that it still contained 46 chromosomes.

#### **PATHOLOGY OF CHROMOSOMAL ABERRATIONS**

The discovery of relationships between aberrant karyotypes and specific diseases has raised some entirely new questions in pathology. Previously it had been generally believed by geneticists that, in man, chromosomal aberrations would be lethal although in plants they are quite well tolerated. Now that aberrant states are known to be common in man the knowledge obtained from studying comparable states in lower organisms may be helpful in understanding the new pathological problems.

Chromosomal alterations differ from single gene changes in that they are not errors of instruction which lead to failure or inefficiency in particular biochemical tasks. Here the genes are presumably normal and efficient but they are wrongly arranged, sometimes providing three or four instructions at the same locus instead of two, sometimes only one and sometimes none at all. The effect on the organism can be, in general, described

as one of dosage (Stern, 1943) Unfortunately the mechanisms behind dosage effects of genes are quite obscure even when the effects of the genes themselves are predictable The influence of X-chromosomes in *Drosophila* is believed to depend upon a balance between them and the autosomes Aberrations in number of X chromosomes alter the sex quantity and the manifestation of sexual traits When an autosome is trisomic or monosomic, however, the morphological peculiarities are less predictable In *Drosophila* the small fourth chromosome can exist in trisomic state in a functional breeding fly Unlike the mongol in man, the trisomic fly is a little larger than the normal A monosomic fly with only one fourth chromosome is also known and this is smaller than normal (Sinnott and Dunn, 1925) In plants trisomy is not uncommon and a complete set of trisomic types corresponding to all 12 gene pairs of *Datura* was investigated by Blakeslee (1923) None of these examples has been studied biochemically and all that is known is that, in trisomy, the manifestations of hereditary characters are distorted The extra dosage of genes on the trisomic chromosome perhaps may be directly discernible in greater concentrations of proteins of the types manufactured from their instructions but this is uncertain Polyploid cells of plants and animals are often larger than the normal diploid cells and they are supposed to contain relatively more water Some of the morphological peculiarities in mongolism may be occasioned by the fact that the cells are never exactly the size suitable for the structures which they are required to build

Somewhat more is known about the pathological states which predispose to chromosomal aberration because their study is included by geneticists as a branch of cytology The process of non disjunction can be brought about by a great variety of agencies but, in meiosis, the key seems to be interference with the normal process of pairing of homologous chromosomes Non disjunction was first observed by Gates (1908) in *Oenothera* hybrids which contained chromosomes unable to pair because derived from different species Inversions and translocations make pairing complicated and more difficult and so they may predispose to non disjunction of chromosomes in an individual heterozygous for such alterations Some such



explanation might account for the pedigree of mongolism, leukaemia and XXXXY recorded by Miller, Breg, Schmickel and Tretter (1961). Moreover, besides the possible presence of "sticky" genes, which disturb the processes of cell division both in meiosis and mitosis, there are physical agencies, such as dehydration, which can produce the same result. The most important known aetiological factor in triple-X females, mongolism, and the other examples of trisomy so far described, is maternal age. The cytological process which is modified by age so as to produce non-disjunction, however, is still purely a matter of conjecture.

## CHAPTER X

### ENVIRONMENTALLY DETERMINED DISABILITIES

*Introduction—Prenatal Mechanical Injury—Radiation—Maternal Nutrition and Effects of Chemical Agents—Foetal Infections in General—Congenital Syphilis—Congenital Toxoplasmosis—Maternal Rubella—Maternal Foetal Incompatibility—Birth Injury—Hypoxia and Hyperoxia—Postnatal Injury—Postnatal Disease—Psychological Factors*

#### INTRODUCTION

THE manner in which nature and nurture interact in the causation of mental defects has been discussed in Chapter IV. To a certain extent every disease is the product of inherited susceptibilities and environmental agencies. The origins of both types of influence are accidental and the main differences between them are the points of time in the life cycle at which they act. In the intervening chapters the emphasis has been upon the description of those conditions associated with mental subnormality which have their origins in events which have taken place before fertilization of the ovum is completed. Any event that affects development after that moment can be classed as environmental. An event might occur earlier, as in the case of maternal syphilis or abnormal antibody formation, but since its influence is exerted on the foetus only after fertilization it can be considered to be part of the foetal environment.

Environmental influences which have adverse effects upon the foetus are very numerous and many of them are liable to cause damage to the central nervous system and lead to defective mental development if the infant survives long enough for this to be seen. Traumata at birth and postnatal accidents or diseases are also important environmental causes of mental retardation. These conditions are separately discussed in the present chapter and their importance is shown to be primarily clinical rather than biological. Indeed, in most instances, it can be assumed that heredity as a cause is insignificant. However,

some types of congenital malformation are experimentally induced by trauma or poisons more easily in some stocks than in others and even the liability to infectious disease may be subject to genetical variation

#### PRENATAL MECHANICAL INJURY

Mechanical injury to the foetus, before birth, has been postulated by some writers as a cause of malformation or of cerebral haemorrhage but, in the absence of more evidence, such views must be treated with scepticism Jansen (1932) attributed deformities, which had their origins in the very early months of pregnancy, to pressure due to abnormal smallness of the sac containing the amniotic fluid Increased pressure could cause stagnation of the blood in the developing bones and lead to all kinds of osseous malformations Van der Scheer (1927) transferred the same explanation to mongolism The traditional theory that skeletal and other deformities can be caused by amniotic bands is subject to the same uncertainties as that of Jansen Even if amniotic peculiarities are considered to be specific causes, we are no nearer to an understanding of the nature of the pathological process until it is known why the structure of the amniotic sac should be anomalous

Another kind of intrauterine injury has been postulated by Schreiber (1939) in which the pathological effects on the foetus are thought to be due to chronic anoxia Continuous anoxia, in cases of maternal mitral stenosis or frequent maternal convulsions, is credited with causing degenerative changes in the *foetal nervous system in the late months of pregnancy* The type of lesion supposed to be produced in this way is diplegia Other anoxic effects on the foetal brain have also been considered as possible causes of foetal damage (Courville, 1959) These include effects acting through the maternal circulation (such as anaemia, toxæmia, hypotension or the action of anaesthetics), through the placenta (such as infarction or premature separation) or through interference with circulation via the umbilical cord (such as coiling of the cord around the neck or knots in the cord) Somewhat similar views have been put forward from time to time as to the possible dangers to the child in prolonged labour De Haas, Quinn and Pryles (1961), for example, have suggested enforced delay during the

second stage of labour as a possible cause of brain damage and mental defect. During prolonged labour the supply of oxygen to the brain may be reduced to a low level by compression of the cord or by other mechanical processes. These dangers are particularly great in cases of prematurity. Premature infants according to MacGregor (1943) are liable to asphyxia which may lead to subarachnoid and interventricular cerebral haemorrhage (see pp. 239-43).

Attempted abortion by whatever means can be considered as another possible cause of intrauterine injury and malformations in surviving foetuses. Adequate information is difficult to obtain in these circumstances and the available data are indeed scanty. Whitehouse and McKeown (1956) interviewed 40 mothers of anencephalics shortly after the birth of whom two admitted attempts to procure abortion. The authors point out that this incidence of attempted abortion (two in 40) was within the usual range for the population in general. Aminopterin (4 amino pteroylglutamic acid) used as an abortifacient has been implicated in the causation of multiple congenital malformations (Warkany, Beaudry and Hornstein 1959). Direct physical foetal injury was reported by Grebe (1955).

## RADIATION

Irradiation may produce deleterious effects on offspring by acting on the germ cells to induce new mutations (see Chapter IV) or by damaging the foetus in the early stages of pregnancy. Both are environmental effects though in the former instance they operate through the production of genetical alterations.

The development of the fertilized ovum in its very early stages can be interfered with by the action of X rays. Cases have been reported in which very large therapeutic doses of X rays have been given in the second month of pregnancy with the object of producing an abortion (Goldstein and Wexlar 1931). There was a direct effect on the foetus and miscarriage invariably resulted. Examination of the embryo showed in some cases colobomatous clefts of the retina associated with neuroepithelial tumours. Murphy (1929) found evidence that therapeutic maternal irradiation during pregnancy might not produce abortion but could still affect the growing embryo. In a series of 74 recorded cases there were only 36

normal children born, 23 imbeciles with heads of abnormal size and 15 offspring otherwise malformed or diseased. The effect, however, must be a rare one, for no instance of therapeutic maternal irradiation was found among 546 pregnancies terminating with malformed offspring investigated later by Murphy (1947). Courville and Edmondson (1958) noted that over 60 instances of mental defect, consequent upon exposure of the foetus to irradiation in utero, have been mentioned or described by various authors. They reported a case of an imbecile child in whom post mortem examination revealed a diminutive brain with simple convolitional pattern and diffuse loss of nerve cells.

The exposure required to produce malformation is at least 100 times that used for ordinary X-ray photography. Experimental results have confirmed this for Russell and Russell (1954) have induced malformations in mouse embryos by exposing the pregnant mothers to doses of radiation ranging from 25 to 400 r.

Radiation hazards to the foetus from atomic explosions are also known. Plummer (1952) reported seven instances of microcephaly and mental retardation among 11 surviving children exposed, during the first half of intrauterine life, within 1,200 metres of the Hiroshima atomic bomb blast. Yamazaki, Wright and Wright (1954) studied the effects of the Nagasaki atomic explosion. This revealed a higher incidence of foetal, neonatal and infant mortality, and of mental retardation in surviving children, among pregnant women with one or more "major" signs of radiation disease (epilation, oropharyngeal lesions, purpura or petechiae) compared with other women.

#### MATERNAL NUTRITION AND EFFECTS OF CHEMICAL AGENTS

Animal experiments reported by Warkany (1947), Millen and Woollam (1959), Giroud (1953-1960) and many others have demonstrated that maternal nutrition in the early stages of foetal growth is a decisive factor in producing certain abnormalities. Deficiency of vitamin A, or of members of the B complex, is especially significant. Excess of vitamin A also may cause damage. Murphy's (1947) survey of pregnant women showed that diets deficient in calcium, phosphorus and

vitamins B, C and D were common among pregnancies leading to foetal malformations. Wartime conditions have provided some evidence of the harmful effects to the human foetus of gross maternal undernutrition (Smith 1947, Antonov 1947). The many other severe physical and psychological stresses prevailing at these times have to be considered in evaluating results.

Possible damage to the foetus also can follow maternal chemotherapy during pregnancy. Antibiotics are not infrequently anti mitotic and they can disturb growth. Gross malformations, particularly of the limbs have occurred in foetuses after the mother took doses of a sedative, thalidomide, in the early stages of pregnancy (Spiers, 1962). Steroid therapy is believed to be sometimes harmful to the foetus but there is in man, little satisfactory evidence for this assumption. Moreover, normal foetuses have been reported after maternal treatment with large doses of cytotoxic drugs during pregnancy (Smith, Sheehy and Rothberg 1958). There have been several reports of defectives born to mothers who had thiouracil while pregnant (Elphinstone 1953, Morris, 1953), though many mothers have had such treatment without apparent adverse effects on the foetus. It is noteworthy, in this connection that Woollam and Millen (1958) found in rats, that methylthiouracil, given in conjunction with excess of vitamin A, resulted in more brain malformations in their young than excess vitamin A given alone. Litters from rats receiving thiouracil alone showed no brain deformities.

The rat has proved to be a satisfactory experimental animal for studies of the effects of chemical agents on foetal development and many such studies have been reported. Gillman and others (1948) have produced hydrocephalus and spina bifida by saturating the maternal tissues with trypan blue. Haskin (1948) noted cranial faults, absence and fusion of digits, cleft palate and other malformations in foetuses whose mothers were injected with a nitrogen mustard compound. Protamine zinc insulin given throughout pregnancy, in doses near to the maximum tolerated, has led to skeletal abnormalities in the foetuses (Lichtenstein, Guest and Warkany, 1951). Salicylates in very large doses during the early stages of pregnancy have been shown to produce cranial and other malformations.

(Warkany and Takacs, 1959) Actinomycin D (Tuchman-Duplessis and Mercier-Parot, 1960) causes gross foetal malformations with doses well tolerated by the mother. It is uncertain to what extent, if any, these effects are applicable to man.

#### FOETAL INFECTIONS IN GENERAL

The passage of pathogenic organisms from the mother to the foetus, though fortunately not common, has been recognized as an established fact for more than two centuries. Duttel (1702) was able to gather together the evidence for transmission of smallpox (variola) to the foetus because of the striking effects produced by the eruption on the foetal skin. Sometimes the mother is immune and shows no sign of the disease and yet she is able to transmit it. Smallpox transmitted by the mother is not known to cause mental sequelae in the child. A considerable list can be compiled of other infectious diseases which have been known for a long time to be transmissible to the foetus. Ballantyne (1902) reported instances in which varicella, scarlet fever, measles, erysipelas and typhoid fever behaved in this way. Mautner (1960) briefly described individual cases with mental defect and other abnormalities whose mothers had scarlet fever, measles, whooping cough or infectious hepatitis during pregnancy. He concluded that these individuals suffered from "infectious embryopathy". However, the evidence for a causal connection between the maternal infection and the defects in the offspring is unconvincing. Foetal anthrax and tuberculosis are also known. No certain instance is known where transmission of bacterial disease from mother to foetus has caused mental defect. Among other organisms which can penetrate to the foetal tissues, but which are doubtfully responsible for mental deficiency, are malaria parasites. Most important in the study of mental deficiency are the diseases which specifically cause cerebral involvement. Though in most cases of cerebral infection the foetus dies *in utero*, a few may survive and, if so, mental defect will be a probable result.

Congenital syphilis is the classical example of intrauterine infectious disease associated with mental defect. The *Treponema pallidum* can actually enter the embryonic substance, if this happens early, miscarriage is produced and, if later on in

pregnancy, the child is born with signs of congenital syphilis. When the foetal resistance is higher or the infection milder, the effects of the disease may not be shown until later, as in congenital general paresis. According to Moore (1941) a woman with untreated syphilis has only one chance in six of having a normal child, further details are given on p 233-5

Protozoal parasites can also pass through the placental barrier. Prenatal malarial infection is known and also maternal transmission of toxoplasmosis. *Toxoplasma* is a protozoal parasite rarely found in man, but cases are definitely known where it has infected the foetal nervous system and caused progressive destruction, leading to idiocy details are given on p 235

Virus infections are sometimes transmitted by the mother and may do great damage to the foetus. Equine encephalomyelitis (Medovy, 1943) has been diagnosed in exceptional cases. In some instances, as, for example, that described by Roback and Kahler (1941), the foetus is found to have suffered from encephalitis though the causative organism cannot be ascertained with certainty. The discovery of harmful effects of maternal rubella on the foetus in the early months of pregnancy (see p 236) has focused increased attention on the possible hazards of other virus infections in pregnancy. Cytomegalic inclusion-body disease can be transmitted transplacentally and lead to mental defect. Many organs may be affected. Evidence of cerebral involvement, in addition to subnormality, include convulsions, abnormalities in head size and periventricular calcification on X-ray (Crome, 1961). In an extensive Swedish survey of over 20,000 pregnancies, by Gronvall and Selander (1948), maternal rubella was reported in 28 cases, two of which ended in abortion, 25 resulted in healthy infants and only one child was malformed. Nevertheless, taking all acute virus diseases together, these were found to have occurred 10 times as frequently among mothers of malformed infants as in the whole sample. Maternal mumps had the worst record, with five malformed infants and one abortion out of 34 cases, and poliomyelitis came next. In a prospective study of 87 pregnant women with poliomyelitis, Stegel and Greenberg (1956) found no evidence of an increase in congenital defects in the offspring, and inconclusive evidence of an increase in prematurity. In respect of the possible hazards to the foetus of maternal



influenza, there have been conflicting reports. Coffey and Jessop (1959) found that pregnant women in Dublin, who were thought to have had Asian influenza during the 1957-8 epidemic, bore children with congenital deformities 2.4 times as frequently as mothers in a control group. The abnormalities were almost entirely of the central nervous system, with anencephaly as the commonest. Doll, Bradford Hill and Sakula (1960), on the other hand, found no increase of congenital abnormalities among the offspring of women, in north-west London, thought to have had Asian influenza and pregnant during the epidemic. Possibly some infants are naturally resistant to these diseases but others are susceptible. Addair and Snyder (1942) have brought forward some evidence which suggests that a recessive gene may cause increased susceptibility to poliomyelitis in children. Some of the differences in foetal resistance to infection may similarly be of genetical origin.

Experimental evidence of infection with virus diseases has been reported by Hamburger and Habel (1947). Microcephaly and impairment of growth of the entire embryo were produced, by injecting 48 hour chick eggs with influenza A, with great consistency. When injection was made at 4 days, the embryo died but was not malformed. Mumps virus did not produce specific malformations, but raised the incidence of types produced in uninfected eggs and was lethal in its effects. Adams and others (1956) reported a reduced pregnancy rate and increase in foetal abnormalities among mice inoculated with a human strain of influenza virus.

#### CONGENITAL SYPHILIS

The frequency of syphilitic defectives has long been a disputed point. The uncertainty is partly due to the diagnostic unreliability of serological reactions, like the Wassermann and Kahn tests, in congenital syphilis, except in cases with very pronounced lesions. Some of the tests in common use occasionally gave falsely positive results and genuine cases, in which congenital syphilis has been present but has become arrested, can be serologically negative. Also the variety in the characteristic clinical signs is large and some of them, like interstitial keratitis, are late in appearance. A rare type, juvenile general paresis, is discussed on p. 265.

Surveys of institutional defectives to ascertain the incidence of congenital syphilis, based only upon serological tests, have given extremely varied results. Early figures showed an incidence varying from 1.5 per cent to 44.9 per cent (Tredgold, 1929). Subsequent surveys produced figures including 2.5 per cent (Weiss and Izgur, 1924) and 19.8 per cent (Stewart, 1926). Clinical signs of congenital syphilis can be very numerous and variable as Stewart's (1930) survey showed. The signs in the eyes, on which stress has been laid, are interstitial keratitis, chorioiditis, scleritis and pupil anomalies. Nerve lesions are exemplified by eighth nerve deafness, paralysis and hyperactive reflexes. Other physical peculiarities include notched teeth, bossed skull, scars on the lips or nose and poor general physique with anaemia and wasting. It is generally agreed that mental defect due to congenital syphilis is a consequence of spirochaetal invasion of the nervous system, meningo-vascular syphilis and general paralysis with or without tabes are the main clinical groupings (Berg and Kirman, 1959).

In cases where the mental defect is mild and stationary, the responsibility of syphilis is difficult to estimate. Congenital syphilis is sometimes considered, in itself, a part indication for admission to an institution. Blindness, deafness or other disabilities can be contributory causes favouring admission and also, sometimes, supposed or actual immorality. In the Colchester Survey the average intelligence quotient of the patients with congenital syphilis was not significantly different from the general average for all patients. The parents and sibs of the syphilitic cases were no less intelligent than the average for the whole sample of institutional cases. Congenital disease, however, can lower I.Q. by several points, for example, from 50 to 20 in an affected monozygotic twin (Penrose, 1937).

In recent years, there has been a dramatic decline in the incidence of syphilis in England and Wales as elsewhere. Death rates per 1000 live births of infants under 1 year, certified as due to congenital syphilis, fell from 0.45 in 1931 to nil in 1957 (Ministry of Health, 1958). This has been reflected by a fall in the incidence of mental defect from this cause. In the Colchester Survey (1938) congenital syphilis was diagnosed in 51 out of 1,280 cases (4 per cent). Benda (1942) diagnosed congenital syphilis in 80 out of 2000 patients at Wrentham.

State School, Massachusetts, also an incidence of 4 per cent Paddle's (1937) figure for the children at Caterham Hospital, England, was 10 per cent In contrast with these figures, Berg and Kirman (1959) found 12 patients with a history of syphilis among 1900 mentally defective patients admitted to the Fountain Hospital Group, London (0.6 per cent) Only five of these 12 showed evidence of neurosyphilis in the form of changes in the cerebrospinal fluid or appropriate clinical signs

#### CONGENITAL TOXOPLASMOSIS

This disease, though fortunately rare, is of great theoretical interest as it demonstrates incontestably that an infection transmitted through the mother to the foetus can cause severe subnormality The protozoal parasite responsible for the condition was initially observed in 1908, though the first proved example of human infection was reported only 31 years later in a newborn infant (Wolf, Cowan and Paige, 1939) A case was reported in England by Jacoby and Sagorin (1948)

The development of diagnostic serological and skin tests has focused increased attention on toxoplasmosis and a large number of studies have been published Feldman and Miller (1956) analysed 187 cases of congenital toxoplasmosis They found that antibodies tended to persist at significant levels for many years in affected offspring and their mothers No mother had given birth to a subsequent child who was also affected Four fifths of the mothers denied having had any illness during pregnancy

The toxoplasma organism thrives on young growing tissues and an infected infant may harbour the parasite for some years Many tissues may be affected, so that manifestations can be extremely variable Among the commoner, non neurological findings are enlargement of the liver and spleen, jaundice and skin rashes A particular affinity for the central nervous system, as well as the retina, produces widespread destruction there In survivors, this frequently results in convulsions, mental defect, hydrocephaly or microcephaly, and intracerebral calcification Ocular signs include chorioretinitis, which is usually bilateral and particularly common, and, less often, microphthalmia Clinical evidence of the disease may only become apparent some time after birth

Schonfeld and Offerman (1945) have made studies which suggest that cases of defect, unspecified clinically, show an abnormally high frequency of *Rhesus* positive types with an abnormally high frequency of *Rhesus* negative mothers. This implies that the presence of the D antigen in the foetus and its absence in the mother is a cause of mental defect. Later work, however, has not borne out the original contentions, although in rare cases it may be a cause of defect associated with spina bifida (Wiener and Peters, 1946, McKeown and Record, 1960). Pantin (1951) found no evidence of excess of cases of *Rhesus* incompatibility in a large series of defectives studied in England, the result is in agreement with the findings of Book, Grubb, Engleson and Larson (1949) based upon a Swedish population of defectives. An enquiry made by Gilmour (1950) led to the same conclusion, he found incompatibility between mother and foetus even less common among defectives than in the general population.

Nevertheless, there is good evidence that some cases of mental defect associated with kernicterus are due to *Rhesus* incompatibility. This is to be expected as a corollary to the work of Levine, Katzin and Burnham (1941) locating the origin of haemolytic disease of the newborn in maternal immunization. It has been well established for many years that severe haemolytic disease in the foetus produces cerebral injury. The products of the destruction of red blood cells are extremely toxic to the foetus (Hampson, 1929) and are apparently absorbed strongly by nerve cells in the basal cerebral ganglia, causing these cells to degenerate. Although the disease starts during the later months of pregnancy and the affected child may be born jaundiced, it is unusual for the most marked effects to be noticeable until a few days after birth. Some cases of severe neonatal jaundice (icterus gravis neonatorum) die, some appear to recover completely and some have residual signs. The clinical features can vary widely (Crome, Kirman and Marrs, 1955). Among the possible permanent effects are spastic paralysis of the limbs with athetosis, deafness and mental retardation. The degree of mental defect varies from very slight retardation to idiocy. The development of the technique of exchange transfusion has greatly improved the prognosis. Many more children survive and are apparently normal. A few, however,

remain obviously affected. Reported figures for the proportion of hospital cases of defect with *Rhesus* incompatibility vary considerably, Book *et al.*, (1949) found only three cases of encephalopathy among 977 and Berg (1959a) noted 18 such cases among 1,900 defectives, mainly imbeciles and idiots.

Several antigens of the *Rhesus* series can cause haemolytic disease, the most dangerous being D. Fortunately, however, only about one child, in 20 of those who are constitutionally incompatible with their mothers in respect of this antigen, suffers from haemolytic disease (Race, 1946). Again, only a very small proportion of affected children develop mental symptoms in consequence.

By no means all suspicious cases, i.e. those with athetosis and a history of neonatal jaundice, show evidence of *Rhesus* incompatibility on blood typing. Other antigens may play their part also, because, as Waterhouse and Hogben (1947) first demonstrated, incompatibility between mother and foetus with respect to the ABO series of antigens is a cause of diminished viability in the offspring. Surveys of haemolytic disease of the newborn have confirmed the importance of the ABO system in this connection (Shamir and Gurevitch, 1953). Clinical and anatomical abnormalities similar to those found in association with Rh or ABO incompatibility can occur also without evidence of antigenic incompatibility between mother and foetus (Zuelzer, 1960).

The discovery of the significance of maternal foetal incompatibility is of great biological interest. As shown by Haldane (1942), natural selection acts in these cases against heterozygous individuals in a peculiar manner. The equilibrium of many such antigenic genes can be unstable and circumstances can arise in which elimination of the relatively unfit heterozygotes actually causes an increase in the prevalence of the genes which produce the dangerous antigen. This is a paradoxical result from the point of view of traditional ideas about evolution.

#### BIRTH INJURY

During birth itself there are, indeed, many opportunities for cerebral injury. However, in order to prove conclusively that a child has become mentally defective in consequence of injury at its birth, we should need evidence of its mental normality

## HYPOXIA AND HYPEROXIA

The results of asphyxia in relation to the birth process are very difficult to separate clinically from the effects of mechanical injury. An association between intranatal hypoxia and subsequently observed mental retardation does not necessarily prove that the hypoxia is responsible for the retardation, it may be that the hypoxic state is in itself a manifestation of already existing cerebral pathology. Difficulties of this kind, as well as variable definitions and methods of investigation, have led to widely differing estimates of the part played by intranatal hypoxia in the production of mental subnormality. Keith and Gage (1960), for example, in a follow up study, found no evidence of an increase of neurological abnormality or retardation in children who had asphyxia or delayed respiration at birth as compared with a control group. Darke (1944), on the other hand, in his follow-up of children asphyxiated and apnoeic at birth, found them to be significantly retarded as compared with their sibs or parents. Many similar studies have been published with equally divergent conclusions. Structural changes in the brain, not incompatible with survival, have been demonstrated in newborn animals following experimentally induced asphyxial states (Windle, Becker and Weil, 1944).

Hyperoxia also has a bearing on the subject of mental defect because of the association of high concentrations of oxygen used in the neonatal period with retrolental fibroplasia, and the fact that a considerable number of children with retrolental fibroplasia are mentally retarded (Williams, 1958, Parmelee, Cutsforth and Jackson, 1958). So far there is no proof that hyperoxia is, in itself, a hazard to mental development. The effects of factors which call for the use of oxygen soon after birth, particularly prematurity, have to be considered. Patz (1954) produced the characteristic microscopical changes of human retrolental fibroplasia in young mammals exposed to high concentrations of oxygen neonatally, but found no significant difference in their brains when compared with those of controls. Hepner (1956), on the other hand, reported histological brain abnormalities in mice, exposed to high oxygen concentrations within 24 hours of birth but not later. Exposure of pregnant mice to high oxygen concentrations near term produced resorption, stillbirth and, in survivors, delay in hair

appearance, failure of growth and abnormalities in motor performance

During the first few days after birth, a human infant is likely to be sensitive to high oxygen concentrations, this is because foetal haemoglobin persists and it has a higher oxygen carrying capacity than adult haemoglobin

#### POSTNATAL INJURY

Direct injury to the brain, caused by falls or other accidents to a child, is an uncommon cause of mental defect. It was thought to be a factor in only three of 900 idiot and imbecile children (0.3 per cent) admitted to the Fountain Hospital, London (Berg, 1960), a finding in keeping with the observation of Ireland (1877), Blau (1936) and others. In populations of mentally defective patients, including all grades of defect and all age ranges, the role of postnatal injury as a cause of defect is greater. In the Colchester Survey such injury was important in 0.9 per cent of the cases and in Boldt's (1948) series the corresponding figure was 1.5 per cent.

Diagnosis may be difficult and must be based on the history of the case coupled with the most careful neurological examination. Substantial brain damage may occur without loss of consciousness (Strauss and Savitsky, 1934) or fracture of the skull (Fabian, 1956). Abnormal neurological signs may be minimal. Hemiplegia is a likely finding (Holden and le Marquand, 1929). Epilepsy has been estimated to follow about 3 per cent of closed, and about 50 per cent of penetrating head injuries (Phillips, 1954). Fits may not occur for months, and even years, after the trauma (Russell 1942).

Intellectual impairment in postnatal traumatic cases is more often mild than gross, and it may be closely related to behaviour disorder and personality change. Manifestations can include inattention, lack of concentration and indifference, with consequent poor results at school, at work, or on intelligence testing. Newell (1937) found that five, of 20, patients with head injury attending child guidance clinics showed impaired mental efficiency as indicated by poor schoolwork. Rowbotham, Maciver, Dickson and Bousfield (1954) judged eight of 82 children with head injury as likely to have their scholastic careers adversely, and permanently, influenced.

## POSTNATAL DISEASE

A considerable number of postnatal diseases have, from time to time, been regarded as causes of mental defect. As many of these diseases occur in early infancy, there is often great difficulty in attributing the defect conclusively to such a cause because of the uncertainty about the mental level before the illness. The possibility that some coincidentally present cause of mental defect may not manifest itself clinically till some time after birth must also be borne in mind. The position is further complicated by the fact that the patient is frequently not brought to the notice of a mental deficiency expert before the acute illness has long been over. It is then extremely difficult to trace the exact history of mental deterioration and to relate it precisely to the disease to which it has been attributed. Until records are obtainable of routine mental tests done before, and at intervals after such illnesses, the precise effects on intellect will remain doubtful. Nevertheless, there is a good deal of evidence implicating various postnatal diseases in the causation of mental defect.

Many of the acute infectious fevers may give rise to neurological complications, often as a consequence of encephalitis. The situation has been lucidly and comprehensively reviewed by Miller, Stanton and Gibbons (1956) on the basis of an analysis of 419 published reports. Mental deterioration has been shown to be an occasional sequel of measles, chicken pox, scarlet fever and whooping cough. Levy and Perry (1948) thought that as many as 2 per cent of defective patients admitted to a Washington State Institution appeared to owe their intellectual retardation to whooping cough. Experience at the Fountain Hospital, London suggests a much lower incidence of mental defect due to this cause (Berg, 1959b). Nevertheless mental deterioration is probably more frequent following some specific infectious fevers than available data suggest because it may only become apparent some time after the acute illness. As relatively few cases are adequately followed up, the defect, or its link with the original illness may be missed. As a very rare event, mental defect is reported as a sequel to whooping cough immunization (Berg, 1958) or to smallpox vaccination (Schachter, 1958). Other varieties of encephalitis sometimes lead to mental deterioration. Encephalitis lethargica



is a well known example about which details are given in Chapter XI. Further examples are Japanese B encephalitis, Australian X encephalitis and equine encephalitis (Ford, 1960). Encephalitis also occurs quite sporadically and it can lead to mental defect, though most affected children who recover do not suffer noticeable retardation (Brain, Hunter and Turnbull, 1929).

Bacterial infections producing meningitis are also known to result in mental retardation in some cases. All degrees, from mild intellectual deficit to idiocy, can occur. Among 800 consecutive admissions of imbeciles and idiots to the Fountain Hospital, London, Berg (1962a) found 22 cases in which the defect was a sequel to meningitis (2.8 per cent). The causative organism was the tubercle bacillus in 11 cases, the pneumococcus in three, haemophilus influenzae in two, and the meningococcus, staphylococcus and pseudomonas pyocyanea in one case each, the remaining three cases were instances of acute purulent meningitis from which organisms were not isolated. Additional signs were spasticity, hydrocephaly, epilepsy, blindness and deafness. Especially noteworthy is the fact that tuberculous meningitis accounted for half the 22 cases. This disease was almost invariably fatal before the introduction of chemotherapy and was thus not previously seen in clinical practice as a cause of mental defect. As with other infections, the role of bacterial meningitis as a cause of subnormality in a particular environment partly depends on preventive and therapeutic facilities.

In addition to viral and bacterial infections, postnatal involvement of the nervous system by rickettsiae, protozoa, fungi and parasitic worms may produce cerebral damage and hence mental retardation in survivors. Such causes are very rarely established in mental deficiency practice and their contribution to the sum total of mental subnormality is presumably extremely small.

Cases have very occasionally been described of gastroenteritis, associated with severe dehydration, with mental defect and quadriplegia as persisting effects (Crome, 1952, Schlesinger and Welch, 1952). Cerebral damage in such circumstances has variously been attributed to impairment of circulation and anoxia, to dural sinus thrombosis and to electrolyte disturbances.

Lead poisoning is sometimes a cause of mental defect, and instances are reported from time to time (Gibb and MacMahon, 1955, White and Fowler, 1960) The usual form of nervous complication is an acute meningoencephalopathy with clinical features including convulsions, neck stiffness and coma (Wyllie, McKissock and Cathie, 1953) Survivors are often severely subnormal Chronic lead poisoning can appear as a behaviour disorder associated with progressive mental deterioration (White and Fowler, 1960) Manifestations of mental impairment may not be apparent till some time after the original illness (Byers and Lord, 1943) The chelating agent, calcium disodium ethylenediamine tetra acetic acid, is widely regarded as the drug of choice in treatment Its availability emphasizes the importance of diagnosis Even more important is prevention by removal of the hazard from the child's immediate environment.

#### PSYCHOLOGICAL FACTORS

The possible significance of psychological factors in the causation of mental defect has been considered in relation both to the prenatal and postnatal environment With regard to the former, Stott (1957) claims to have established a relationship between various factors operative during pregnancy (including psychological stresses like severe matrimonial troubles) and mental retardation congenital malformation and early ill-health in the offspring These conclusions appear to be based upon insufficient data

A good deal more information has been accumulated on the effects of psychological factors operating after birth Evidence from studies of twins and of children reared in surroundings other than their own home, referred to in Chapter IV, indicate that such factors can be beneficial or disadvantageous in regard to mental development Bowlby (1958) has summarized evidence from many sources of the harmful effects of early maternal deprivation on physical, intellectual, emotional and social development

While there is good evidence that adverse psychological conditions can impair intellectual development and function, the extent of the impairment that can be determined in this way is uncertain Bourne (1955) thought that 10 per cent of cases of

extreme mental defect could be due to perverted infant rearing. This conclusion was based on a study of only 16 defectives in none of which structural cerebral abnormalities were excluded.

## CHAPTER XI

### MENTAL ILLNESS

*General Principles—Epilepsy—Symptomatic Epilepsy—Idiopathic Epilepsy—Psychoneurosis—Psychopathic Personality—Moral Deficiency—Mental Defect and Crime—Administrative Relationship between Crime and Defect—Affective Psychosis—Schizophrenia—Organic Psychosis*

#### GENERAL PRINCIPLES

IT is convenient to distinguish between mental illness and intellectual defect. Failure to make this distinction can cause much confusion. Illness and defect must be considered as two dimensions of variation. Thus, theoretically, a person of any level of intellectual capacity can suffer from any degree of mental illness. The susceptibility to illness may indeed be correlated with intelligence level, in that certain kinds of defect may predispose to epilepsy or psychosis. In epilepsy, for instance, mental illness is part of the symptom complex. Conversely, mental illness, as the primary condition, may contribute to a lowering of intellectual capacity, for example, Dawson and Conn (1931) found that the mean I Q of 49 epileptic children, attending the Royal Hospital for Sick Children in Glasgow, was only 80.6. In order to be logical, we should always attempt to assess what the intellectual level would have been in the absence of the illness. Richards (1951) has shown that cases of schizophrenic psychosis of early onset, occurring on a basis of normal intelligence, can become indistinguishable, on casual observation, from congenital imbeciles and idiots, and are often so diagnosed.

Mental illness, whether in the form of epilepsy, neurosis, psychopathy or psychosis, is a very important contributory factor in the selection of cases for hospital treatment. As shown in Chapter III, the high grade cases admitted to hospitals are only a very small sample of all those of comparable ability in the general population. They require care and control because

they become out of harmony with their social environments, and often this is because they are mentally ill. It cannot be correctly inferred, simply from the high proportion of sub-normal patients who have mental illness, that poor intellectual capacity is a contributory cause of mental illness. The incidence of neurotic and psychotic disturbances at different intelligence levels in the general population needs to be ascertained. Thus, in Dewan's (1948) survey of conscripts, the proportions of well adjusted and psychopathic subjects were compared at different levels of performance on the Canadian Army M-test. A definite association between low test level and emotional instability was found to exist. A factor which would tend to produce such an association is that most mental disturbances tend to reduce efficiency on intelligence tests.

#### EPILEPSY

The mental illness most characteristic of defectives is some form of epileptic seizure. There is a wide range of symptoms that come under this heading, and infantile convulsions are included as well as major and minor fits and other variants. Convulsions in early infancy can occur in a great variety of conditions, some of which are intercurrent, like tetany due to nutritional deficiency, and they are not necessarily indications of abnormal cerebral development. A history of convulsions, however, is frequently obtained for children who, later on, show definite signs of epilepsy or develop into cases of mental defect. Convulsions repeated over a period of weeks or months in early life and petit mal attacks in the first two years are more likely than isolated attacks to be followed by chronic disorder (Thom, 1942).

The use of electroencephalography has enabled Gibbs and Lennox (1938) to show that, in cases subject to petit mal, or minor attacks, which do not lead to generalized convulsions, the normal cerebral rhythm is disturbed. A combination of a slow wave and a "spike", recurring about three times per second, is the characteristic feature. Forced breathing, which artificially lowers the threshold for epileptic attacks, may induce dysrhythmia more readily in epileptic than in non-epileptic subjects. However, in patients subject to major seizures only, it is often very difficult to detect any dysrhythmia by such methods.

## SYMPTOMATIC EPILEPSY

There are two ways of regarding spontaneous epileptic attacks. They can be looked upon as symptoms of underlying cerebral malformation and disease or even of temporary physical and chemical disturbances which interfere with the normal nervous rhythms. This aspect was emphasized by Wilson (1929), who protested against the tendency of neurologists to ascribe a sinister prognosis to every case of epilepsy on the grounds that it was in itself an incurable disease.

The symptomatic kind of epileptic attack is seen in such a condition as *epiloia*. Fits also occur in amaurotic idiocy and other progressive degenerative diseases. In comparatively stationary conditions, like phenylketonuria and cerebral diplegia, epileptic attacks may occur in infancy or early life, but they tend to become much less frequent as age advances. Almost any gross disturbance of cerebral functioning can be accompanied by epileptic manifestations, and, consequently, an association between the severity of mental defect and incidence of fits can be demonstrated.

In the United States and in Canada, where there are separate hospitals for epileptics, defectives who have prominent epileptic symptoms can, for administrative convenience, be treated

TABLE XLII

INCIDENCE OF EPILEPSY AMONG PATIENTS OF  
SPECIFIED CLINICAL TYPES

Type	Number of Cases	Number Epileptic			Total Per- centage Epileptic	
		Certain	Doubtful	Total		
Mongolism	63	0	1	1	1.6	
Endocrine disorder	88	3	10	13	14.8	
Congenital syphilis	50	3	11	14	28.0	
Neurological lesion	128	36	23	59	46.1	
Skeletal malformation	142	20	14	34	23.9	
Miscellaneous abnormalities	87	12	10	22	25.3	
Others {	Idiopathic epilepsy	210	119	91	210	100.0
	Non-epileptic mental illness	204	—	—	—	0.0
	Residual group	308	—	—	—	0.0
All patients	1280	193	160	353	27.6	

primarily as epileptic rather than as intellectually subnormal. In England this procedure is not adopted, and it was possible in the Colchester Survey to compare in the same hospital the proportion of epileptic cases in given categories with one another. Those patients who had quite definite symptoms were classified under the heading of certain epilepsy and those who had merely a history of convulsions or who had seizures of obscure types, such as vasovagal attacks, were classified as doubtful. The results are shown in Table XLII, in which the incidence of epilepsy in different pathological types is set out. Nearly half the patients with neurological lesions had fits of some kind, as did one-quarter of those with abnormalities of the skeleton, including the cranial malformations, microcephaly, hydrocephaly and acrocephaly. With respect to mental grade, most surveys have shown, as might be expected, that epilepsy is a more frequent symptom among low-grade defectives than among the higher grades. Waggoner and Sheps (1944) in a survey of defective subjects, however, found no relationship to intelligence level.

#### IDIOPATHIC EPILEPSY

Epilepsy in the majority of subjects, whether they are of normal or subnormal intelligence, is not classified as symptomatic. The term "idiopathic" has been used in medicine for these cases, in which the cause is largely unknown. There seems to be an inborn tendency to dysrhythmic cerebral activity coupled with absence of any detectable structural abnormality. In a person, who is liable to convulsions of the major type or to the slighter minor epilepsy and who does not suffer from any known physical disease, the epilepsy itself has to be regarded as a primary condition. Idiopathic epilepsy is found in about one to two per 1000 among the general population of school-children (Henderson, 1948). Some estimates are higher than this and there is difficulty in deciding exactly what constitutes the diagnosis. Lennox, Gibbs and Gibbs (1940) found that a very large proportion, e.g. some 10 per cent of normal subjects showed occasional abnormalities on electroencephalographic examination. They also found that an even greater proportion, about 60 per cent., of the relatives of known epileptics had abnormal rhythms. That the cerebral dysrhythmia is in some

way inborn, or part of the somatic constitution, is hardly to be doubted, but its relationship to actual epilepsy is far from clear.

The psychology of epileptics, apart from the fits, is an important study. Stoddart (1926) considered that idiopathic epilepsy is best regarded as a symptom of a special kind of mental illness which sometimes amounts to psychosis. The main peculiarities are to be found in the personality and in behaviour reactions. For example, Freeman (1935) has reported a pair of monozygotic female twins only one of whom had epileptic attacks though both had unusually egocentric dispositions. The epileptic subject is liable to be strongly emotional but also shallow and sentimental. Ideas are stereotyped, narrowness of outlook, self-pity and childish desire for affection and attention are coupled with irritability leading to outbursts of anger and violence. In the intervals between attacks, epileptics can behave very sensibly. It is sometimes hard to believe that a patient who seems so well at one time may quite suddenly, before, after or in substitution for an epileptic attack, become so disturbed as to be dangerous to others.

Should an epileptic subject have the additional misfortune of being scholastically retarded, the double handicap can be sufficient to lower social efficiency to the level of mental subnormality. Thus there is a large class of cases of idiopathic epileptics who require care and control either as defectives or epileptics, according to the prevailing type of administration. In Table XLIII the grades of 210 patients of this kind are shown and compared with the grades in a hospital population of 1,280, the incidence was 16.4 per cent. Males were rather more frequently represented than females. Idiopathic epileptics were distributed over all grades fairly evenly and their mean I.Q. was  $41.2 \pm 22.4$  (Appendix 8).

The influence of epilepsy on intellectual level is not clearly understood. Although many subjects are subnormal the disability is not inconsistent with normal or even exceptional ability. Famous epileptics, like Dostoevsky, have made splendid contributions to human culture. It is sometimes believed that intellectual deterioration is a common consequence of epileptic attacks, but there is little direct evidence of this. There remains the danger that drugs, such as bromides and barbiturates, administered in order to control the fits may



themselves stultify the intellectual processes. One remedy, sodium dilantin, though it has disagreeable effects, like thickening of the gums, appears to be less inhibiting than the barbiturates to the intellectual functions. A few epileptics do show gradual loss of intelligence, but these are cases in which there is either a progressive organic disease or a marked degree of psychosis. In a survey of 85 epileptic defectives over a period of 10 years, Falk, Penrose and Clark (1945) were unable to demonstrate any consistent fall in IQ, except in the case of three patients who were psychotic as well as defective.

The conditions grouped under the heading of idiopathic epilepsy are not homogeneous. In the first place, there are widely different degrees of severity and frequency of attacks in different subjects. This fact puts genetical investigations on very uncertain ground. A recessive condition has been described by Lundborg (1903), known as myoclonus epilepsy because of muscular twitchings which occur even in the absence of fits. The disease is not characteristically associated with mental debility. Many investigations have been carried out on the familial concentration of epilepsy in general. Among the most extensive studies are that of Conrad (1935) and those of Rosanoff, Handy and Rosanoff (1934) on twins. In the Colchester Survey,

TABLE XLIII

DISTRIBUTION OF CASES WHOSE MAIN SYMPTOMS WERE THOSE OF  
MENTAL ILLNESS

(Colchester Survey 1938)

Diagnosis of Mental Illness	Mental Grade				Total
	Dull	Feeble minded	Imbecile	Idiot	
Idiopathic epilepsy	30	57	81	42	210
Psychoneurosis and perversion	56	53	20	3	132
Affective psychosis	4	17	3	0	24
Schizophrenia	8	11	16	13	48
Total mentally ill	98	138	120	58	414
Total population of patients examined	179	448	433	220	1280

six patients among the 210 idiopathic epileptics had first cousin parents, a proportion high enough for suspicion of recessive determination to be reasonably entertained. When idiopathic epileptics are taken together as a group, their relatives do not show a high incidence of the same condition. For example, the incidence of epilepsy in relatives of the same group of 210 was only one and a half times as high as the incidence in relatives of patients otherwise classified. The excess was statistically significant in view of the large numbers involved but not very striking in practice.

We might assume that there are genes which lower the threshold to stimuli normally insufficient to cause seizures. The genes might act by making slight structural or chemical changes in the nervous system which predisposed to dysrhythmia. To some extent the question is always a matter of degree because strong enough stimuli, such as electric currents passed through the cerebrum will produce a convulsion in anyone. There are well established examples of inherited predispositions to fits, spontaneous or induced, in rodents. One other good instance concerns the spontaneous convulsions which occur in Viennese white rabbits. This peculiarity has been shown by Nachtsheim (1939) to be recessively inherited.

### PSYCHONEUROSIS

Relatively mild though often very chronic types of mental illness, such as obsessional neurosis, anxiety states and hysteria probably occur just as frequently in defectives as in the population at large. These psychoneuroses differ from the psychoses in that they respond well to psychological treatment whereas the psychoses do not. Psychoneurotic disabilities add to the complications of supervision of defective patients of all grades and types, and from time to time, they contribute to these patients' being considered subnormal. Neurosis can hardly be credited with being a cause of intellectual defect and, in contrast to epilepsy, it is not a natural consequence of disease of the central nervous system. Nevertheless a neurotic child may not do himself justice in a test of intelligence and may thereby be wrongly rated. A competent psychometrician will be on the alert to detect an anxiety state which interferes with test performance. Part of his work is to allay such anxiety and to obtain the

patient's confidence before making a report on the intelligence level

The relationship of psychoneurosis to the more serious forms of mental disturbance, which lead to social incompetence, is not a simple one. Some cases, where theft, violence or arson may be due to underlying obsessions or phobias, are susceptible to psychotherapy. When children, whose intellects are subnormal, commit neurotic misdemeanours they are more likely to be found out than children of greater ability. They are easily led by more skilful malefactors and are sometimes suggestible enough to be made to perform the parts of scapegoats.

The neurotic states are among the factors which contribute to the causes of antisocial behaviour disorder in patients, who swell the numbers of high-grade defectives in hospitals, and may account for 10 per cent of all admissions. The distribution, with respect to mental grade, of all cases in the Colchester Survey whose main symptoms were of mental illness is shown in Table XLIII. In the absence of mental illness, these cases would all have been diagnosed acclinical or residual. The concentration of neurotics among the higher-grade cases is noteworthy and, in these patients, neurosis was the main reason for admission.

Closely allied to the psychoneuroses are sexual perversions, which include aberrations ranging from indecent exposure to homosexuality. These occur with considerable frequency among defectives, as indeed they do also in every section of the population. Their apparent prevalence among defectives may be simply the consequence of failure of concealment. Bestiality is a charge which sometimes is brought against a defective but little is known about its prevalence generally. The fact that sexual irregularity, like promiscuity and incest, occurs not very uncommonly in the families of defectives may indicate that the patients concerned are drawn from social strata in which the canons of behaviour are less restrictive than in the rest of the population. From the biological point of view, this relative lack of sexual inhibition may be connected with the high fertility believed to be possessed by the subnormally intelligent. If so, it could be looked upon perhaps as part of the normal biological equilibrium rather than as evidence of moral depravity.

The genetics of the psychoneuroses has been but little studied, partly on account of the elusive nature of the facts and partly because marked changes in psychological reactions can be produced by environment. Brown (1942) analysed records of relatives of neurotic patients and Slater (1943) compared family histories of men referred for psychological symptoms in the army with a control group. Pollock, Malzberg and Fuller (1939) made an extensive study of the familial incidence of all kinds of mental disorders, including the psychoneuroses. The outcome of all these enquiries has been to demonstrate some degree of familial concentration of neurotic traits, but the significance of this concentration is not necessarily genetical. Moreover, there is no indication of any genetical association between neurosis and intellectual defect. The view held by Lng (1940) that male homosexuality is produced genetically by a factor which turns females into males, the opposite of testicular feminization, is not supported by adequate evidence. Darke's (1948) study of 100 sibships containing male homosexuals gave no encouragement to the theory. Furthermore, Barr and Hobbs (1954) found normal absence of sex chromatin in cells from male transvestites. The significance of Slater's (1962) finding that male homosexuals are born at unusually late maternal ages is not yet clear.

#### PSYCHOPATHIC PERSONALITY

There are certain types of mental illness characterized by antisocial behaviour, not amounting to insanity as generally understood, which do not respond readily to psychotherapy. These are often classed under the broad heading of psychopathic personality, a diagnosis which has been interpreted in a variety of different ways (Curran and Mallinson, 1944). The name implies that the antisocial patient is recognized to be mentally ill and should be treated as a medical problem rather than as a case for retributive punishment. This principle has formed the basis of the definition of a psychopathic person in the 1959 Mental Health Act. People with psychopathic personalities are by no means always intellectually retarded. Excellent descriptive case histories have been given by Burt (1925). Repeated antisocial acts can sometimes be interpreted as evidence of profound mental disturbance of a schizophrenic

variety, as part of an epileptic psychosis or of organic disease, such as encephalitis lethargica.

Psychiatrists are often in doubt as to the correct description of a given mental illness and there is a natural tendency to make an inclusive category for the residual clinical material. Patients diagnosed as having psychopathic personality undoubtedly form a heterogeneous group. They include pathological liars, thieves, sex perverts, drug addicts, and so on. The common factor, which they share with one another, of relative immunity to social influence and refusal to learn by experience points to the conclusion that these patients are more closely allied to psychotics than to neurotics. In a home or hospital, their training is a long and arduous process with prospects of repeated disappointments for those under whose care they are placed. It is, however, well to note that punishment has no beneficial effect and is likely to be harmful. As Alexander and Staub (1929) have shown, antisocial acts can arise from deep unresolved feelings of guilt, which punishment may fortify. Very little is known about the contribution of genetical factors to the causes of psychopathy, during recent years much stress has been laid on the suggestion that deprivation of maternal affection may be a potent environmental factor.

#### MORAL DEFICIENCY

It was largely with a view to the control of cases of psychopathic personality, combined with mild intellectual defect, that the, now obsolete, British Mental Deficiency Acts of 1913 and 1927 included the category of "moral deficiency." Such persons were defined, in 1927, as those "in whose case there exists mental defectiveness coupled with strongly vicious or criminal propensities, and who require care, supervision and control for the protection of others."

The justification for the concept of moral defect was the belief, widely held in the latter part of the nineteenth century, that criminals represented a variant of humanity degenerate morally, intellectually and physically. The protagonists of this theory, whose work under the name of "criminal anthropology" has been summarized by Havelock Ellis (1890), exerted an influence upon the experts who drafted the Mental Deficiency Acts. Anatomists, such as Broca, and early students of human

heredity, like Prosper Lucas and Morel, laid the foundation of criminal anthropology and initiated an enormous amount of measuring of prisoners. In a paper read at the British Association, Wilson (1869) proved that habitual criminals must be morally defective by showing that their heads were abnormally small. All manner of physical peculiarities were taken into account, in a similar fashion, by observers in France and other European countries, until the apex was reached in the work of Lombroso (1887) of Turin. Some weaknesses in the theory were revealed by Galton, who suggested that composite photography of criminals should reveal the features common to all members of the class. Actual experiment showed that composites of criminal faces, particularly of those who were defective and insane, gave rise to pictures rather pleasing and noble, both in feature and expression, which could pass for rather blurred but not uncomplimentary portraits of ministers of religion. The fundamental factor common to all kinds of criminals is that they are all human. Finally, Goring (1913) published a very complete survey of convicts in Parkhurst Prison and expounded the view that, though the criminal was, on the average, physically and intellectually inferior to the man who arrested him, a criminal type did not exist. Controversy persists, however, at the present day. Claims that there are physical stigmata for criminal behaviour (Hooton 1938) are becoming less ambitious than formerly and they are strongly disputed. Hrdlicka (1939) stated definitely that there are no physical signs by which a prospective criminal can be recognized.

If there is no criminal type, it follows, almost as a formal corollary, that there is no morally defective type. The search for specific inheritance of criminality or moral defect is therefore senseless. Goring (1913) demonstrated that close relatives of convicts, that is to say, their brothers and parents, were more likely to be convicted of crime than were members of the general population. Also the proportion of sibs convicted was increased if one or both parents had been convicted. Furthermore, there was evidence of assortative mating of criminals. Surveys of twin sets of convicts, carried out by Lange (1929) and by the Rosanoffs (1931), indicated that hereditary constitution was of considerable importance in the chain of events leading to conviction. Nothing more definite than this

can be reliably concluded. It is impossible here satisfactorily to disentangle the genetical factors from the influences of social environment. Undoubtedly low economic status produces conditions more favourable to the growth of delinquency, in a population, than comfortable surroundings (Jenkins and Brown 1935). Many valuable statistical facts are presented in the report by East, Stocks and Young (1942) which plainly reveal the complexity of the problem. In so far as mental illness or defect predisposes to crime and in so far as these disabilities are inherited, so also could criminality or delinquency be inherited, but this is a very remote connection with the direct effects of genes.

#### MENTAL DEFECT AND CRIME

The overlap between mental deficiency and criminality can be studied by finding out how frequently criminals can be considered defective. Goring (1913) showed that men convicted of theft, arson, wilful damage to property and sexual offences were less intelligent than violent criminals and considerably less intelligent than embezzlers, bigamists and other perpetrators of fraud (see Table XLIV). In a survey of 309 adolescent delinquents, Stefanescu-Goanga (1939) found 99, or 32 per cent, mentally defective; among those convicted of homicide or theft, the proportion of defectives was even higher. Though Frankel (1939) estimated that only 15 per cent of 1000 murderers were noticeably defective, the mean mental age of 722 tested members of the group was only 11 years, equiva-

TABLE XLIV  
RELATION OF TYPE OF CRIME TO MENTAL GRADE  
(after Goring 1913)

Crime	Number of Cases	Number Defective	Percentage Defective
Violence to property (theft, burglary, arson, wilful damage)	402	58	14.4
Sexual offences (rape, perversion)	101	13	12.9
Violence to person (murder, manslaughter, robbery with violence)	219	17	7.8
Fraud (forgery, embezzlement, bigamy)	226	7	3.1
Total . . .	948	95	10.0

lent to an I Q between 70 and 80, so that many must have been intellectually dull

Taking criminals of all types together, Paulthorpe (1932) estimated that 15 per cent were defective, whereas East (1944) gave a corresponding figure of only 0.5 per cent. Goddard's (1914) early estimate for the same percentage in the United States was 55, but Thompson (1940) reported that only 2.4 per cent of sentenced offenders in New York were mentally defective, though he also stated that 6.9 per cent had psychopathic personalities. The proportions rated defective depend upon the current definitions of mental defect and also upon the ages of the subjects. Burt (1925) pointed out that among juvenile delinquents 7.6 per cent could be accurately rated defective, but that 25 per cent were dull and an even greater proportion were educationally backward. East, Stocks and Young (1942) found a total frequency of mental retardation of 14.7 per cent among 4000 delinquent boys.

In all known data, male criminals predominate numerically over females, especially where crimes of violence are concerned. This is a point to be remembered when we observe the greater numbers of females recognized to be defective in the borderline groups. To some extent the provision of accommodation in prisons is complementary to provision of beds in mental hospitals of all kinds. For example, a young, adult, mentally retarded male may commit a crime of violence and be sent to prison, whereas a female of the same age and grade perhaps becomes sexually promiscuous and is considered mentally defective.

#### ADMINISTRATIVE RELATIONSHIP BETWEEN

##### CRIME AND DEFECT

The standards by which defect is recognized in different communities react in a remarkable way on the proportions of cases admitted to hospitals as compared with those sent to prisons or reformatory institutions. On the whole, if trouble is taken to recognize and to treat the defectives, the number of prisoners is reduced. Thus in the states of New York and Utah, where the annual admission rates to hospitals for defective and epileptic patients were 20 per 100 000 inhabitants in 1935, about 23 persons per 100 000 were received from courts into state



prisons. In States admitting fewer defectives, more prisoners were received, and in Arkansas, Arizona and Nevada, where no defectives were reported, the average number of persons received, per annum, into state prisons was about 66 per 100,000 (Penrose, 1943). This effect is partly attributable to administrative differences in relation to white and coloured populations. More attention is paid to the problem of mental defect among the white than among coloured delinquents.

The same relationship can be observed if all types of mental abnormalities are grouped together. In the Union of South Africa, for example, administrative differences are very noticeable when the European and non European populations are compared, as in Table XLV. The total proportions of cases requiring care and control are not very different in the two

TABLE XLV  
INSTITUTIONAL POPULATION OF UNION OF SOUTH AFRICA IN THE YEAR 1935  
(Penrose 1943)

Population	Number of Inmates of Mental Hospitals per thousand of the popula- tion	Number of Prisoners per thousand of the population	Total
European	3.27	0.45	3.72
Non European	0.82	2.56	3.38

groups, but among Europeans the diagnosis of mental illness or defect predominates whereas, among the coloured populations, behaviour disorders are most frequently classed in the category of crime. In European countries there is marked variation in the provision of beds for mentally ill and defective people. The gradient shown in Table II (p. 21) is correlated with an inverse gradient representing the number of convictions for serious crimes or of prisoners. That is to say, there is an inverse relationship between the number of beds provided for the mentally ill or defective and the number of people in prison (Penrose, 1939c). This appears to be true for each age group. On the average, the provision of two mental hospital beds will make one prison cell unnecessary. Per inmate, prisons are about twice as expensive to run as mental hospitals so that, even on financial grounds, there is no loss in treating delinquency as a medical rather than as an ethical problem.

In administrative practice there is considerable difficulty in deciding how best to provide for delinquents, who are not enough retarded for them to be regarded as mentally defective on intellectual grounds alone. The legal solution of providing a category of moral deficiency has not proved to be very useful. In the first place, the implication that there is a type of individual with genetical absence or weakness of morals is not in keeping with scientific observations. Secondly, the legal confusion of delinquency with intellectual incapacity has led to the saturation of hospitals for defectives with high grade patients, selected on account of antisocial behaviour. The juxtaposition of these psychopathic cases with the well behaved patients, who are definitely inferior mentally, is unfavourable for the efficient training of both groups. The solution suggested by many investigators is that high-grade defective delinquents require separate hospitals (Dybwad, 1941). Humphreys (1940) recommended that special institutional provision should be made for psychopathic defectives because this is needed in any case for a small proportion of defectives. The care of these cases could be combined, with the care of other psychopaths, who are merely dull or scholastically retarded, more easily than with the amenable defective patients. Such procedures might be more favourable to the scientific investigation and treatment of delinquency than methods which are based upon a confusion between intellectual defect and disordered personality.

#### AFFECTIVE PSYCHOSIS

Among cases of mental defect seen in hospitals, a few patients are found who suffer from manic and depressive states. Only very rarely are these patients sufficiently ill to warrant their transfer to hospitals for mental illness. In a person of low intellect, it is difficult to distinguish a mild manic attack from a manifestation of hysterical neurosis. Indeed it is characteristic of manic and depressive states in defectives that they are rather milder than in people of average mental ability. Myerson and Boyle (1941) and others have expressed the view that the true manic depressive states occur only in people of average or superior ability. This may be reasonably doubted but it seems to be true that the symptomatology of affective disorders alters with the intellectual level. In the concepts of Freud (1925),

the ego, and consequently the super-ego, is weak in people of subnormal intelligence. Thus the conscious and unconscious feelings of guilt and unworthiness, characteristic of the affective disorders, engendered by hypertrophic super-ego, are lessened. True manic depressive psychosis in an idiot is practically unknown. When manic states occur in defectives, they may be accompanied by visual hallucinations, which are rare phenomena in average subjects. Mild chronic mania is not uncommon. It should be remembered that most defectives are young at the time of ascertainment and that affective psychoses are usually diseases of late or middle life and are unlikely to contribute to the diagnosis of defect.

As already mentioned (Chapter VIII p. 194), manic depressive disease tends to be transmitted from parent to child in some families in a manner suggesting that a single heterozygous gene is the main cause. In view of the great variety of different types of affective psychoses which occurs, it seems very improbable that one gene only is responsible for them all. Moreover, acute attacks of mania or depression are often traceable to disturbances in the psychological environment of a subject, so that only the predisposition need be accounted for genetically. The mean age of onset, which is earlier in females than in males, is in middle life and does not seriously curtail the reproductive period. In a mild form, the manic temperament is not incompatible with social and biological success and may even help the individual. The fact that the onset of illness is later in the male than in the female may be interpreted as due to selective modification by nature, because the male reproductive period continues longer than that of the female.

#### SCHIZOPHRENIA

The type of psychosis most intimately associated with mental defect is some form of schizophrenia, there are certain important similarities in the two conditions. In the pure form, originally described by Kraepelin as dementia simplex, a subject initially with average intelligence gradually develops a mental condition which cannot be distinguished, by clinical tests, from a state of profound subnormality (Richards, 1951). If a schizophrenic psychosis arises in early adolescence, normal mental potentialities may actually remain, but it is impossible, by means at

present at our disposal, to revive them Schizophrenia characterized by very early onset, originally called dementia praecocissima by de Sanctis, is an important, though infrequent, cause of mental defect Bradley (1941) made an extensive study of the disease Both boys and girls are affected Deterioration of emotional and intellectual faculties takes a rapid course, it begins as early as 4 or 5 years of age and, in rare cases, 2 years, according to Grebelskaja Albatz (1934) If delusions or hallucinations are present, they are only noticeable in the early stages In order to make the diagnosis correctly, the fact that the child was normal intellectually before the onset of psychotic symptoms must be firmly established Encephalitis and organic degenerative diseases can be excluded as possible diagnoses by the absence of neurological signs The concept of dementia infantilis, introduced by Heller (1930), includes not only the classical cases of infantile schizophrenia or autism but post encephalitic and other organic states (Benda, 1960)

The common types of dementia praecox, in which the disease starts in adolescence or early adult life, do not, or should not strictly, come into the province of mental defect It is, of course, not very unusual to find that defectives who have come under observation on account of behaviour disorders, subsequently develop characteristic schizophrenic psychoses (Rohan, 1946) If necessary such cases can be then transferred to hospitals for the mentally ill

Sometimes isolated symptoms that form part of the characteristic picture of schizophrenia are found in mongols phenylketonurics and other classes of patients Catatonia with waxy flexibility, stuporous states, outbursts of violence, stereotypy, negativism and mannerisms occur in low grade defectives, and their psychiatric significance is difficult to determine Earl (1934) inclines to the view that they are really signs of psychosis Alternatively, they can be regarded as modes of reaction of an infantile nature, which imply that instinctual and emotional development has been retarded along with the intellectual development

Schizophrenia of all types is commoner and of earlier onset in males than in females (Malzberg, 1935) It is also associated with greatly lowered fertility (Essen Moller, 1935, Kallman, 1938), and for this reason must show a recessive rather than a

dominant type of inheritance. There is, however, little uniformity among the patients diagnosed schizophrenic and no single gene can be held responsible for all cases. Some family histories suggest a single autosomal recessive gene as a likely cause (Book, 1953), others a single sex linked recessive gene. The genetical aspect of dementia praecoxissima has received very little attention. Evidently a regularly dominant gene could not be the main cause. Familial incidence in sibships has not been emphasized in the literature, but there remains a possibility of recessive inheritance. Multifactorial inheritance is a possibility and it would account for reported observations such as those of Mitsuda and Ok1 (1958) who found some kind of familial incidence of schizophrenia in three out of eight childhood cases. Most psychiatrists who have studied these very early cases have been mainly on the alert for the effects of environmental crises in the causation. In view of the possible importance of degeneration of the gonads as the primary seat of the trouble in schizophrenic adults (Mott, 1919, Hemphill, 1944), signs pointing in the direction of sex chromosome anomaly might be especially worthy of note in cases of dementia praecoxissima also.

#### ORGANIC PSYCHOSIS

The peculiar form of neurosyphilis which causes insanity in adults is paralleled by a type of congenital syphilis which causes progressive mental defect in children or young adults and which is known as juvenile general paresis. A full clinical description was given by Stewart (1933). The usual history is of a gradual mental and physical deterioration, which begins during school age and in some cases is initiated by convulsions. Occasionally mental retardation is observed in infancy, but usually the intelligence is at first quite normal. The child becomes increasingly stupid, neurotic, indifferent to its surroundings, dirty in its habits and eventually bedridden with contracted limbs, marked emaciation and, in fact, all the features which distinguish the third stage of the adult type. Sometimes, in the early stages, euphoria and mildly grandiose ideas can be observed. Neurological signs characteristic of general paralysis are invariably present. Slurred speech is an important sign and persistent grinding of the teeth is held to be

a symptom of some diagnostic value. As in other forms of syphilitic amentia, the external signs of congenital syphilis may be entirely absent. With regard to the microscopical appearances, treponemata are usually abundant in the cerebral cortex, otherwise the morbid histology resembles that of the adult form. The diagnosis in typical cases is not difficult as the Wassermann test in the cerebrospinal fluid is strongly positive. The disease can be arrested completely by anti-syphilitic measures, such as antibiotic therapy and, formerly, fever treatment. Some degree of intellectual impairment remains although, if treatment is started early enough, the residual effect may be mild.

Familial cases of juvenile paresis are not common but the coincidence of the adult form in a parent with the juvenile form in the child has been reported in the medical literature (Kanner, 1935). Among the adult cases especially, but also among juvenile cases, there are more males than females. It has always been difficult to understand why syphilis should attack one part of the body in one subject and a different part in another. Either the treponema which causes general paresis is a specially neurotropic variant or some people are constitutionally predisposed to react to syphilitic invasion in this peculiar manner. The sex limitation, tending to confine the disease to males, is of genetical interest because there may be families in which females, rather than males, are more likely to be affected.

An important type of organic psychosis connected with intellectual defect is sometimes the aftermath of encephalitis lethargica. Hall (1923) analysed reports on residual mental symptoms in post encephalitic patients, who contracted the disease in the epidemics from 1919 to 1922, and found that severe mental disorder was not a frequent complication. However, changes in moral behaviour were common. In juvenile cases it was common for an affected child, previously normal, to become intellectually stunted and emotionally irritable. Cases of thieving, suicidal and homicidal tendencies had been reported. Dawson and Conn (1926) compared the mean I.Q. for children, who had suffered from encephalitis lethargica, with that for their normal sibs and found that there was a mean fall of 16 points attributable to the disease.

Clinically it is sometimes difficult to be sure of the diagnosis, because severe late results can follow an acute illness which, at the time, was not recognized as encephalitis lethargica. Other forms of encephalitis also may mimic the disease. The development of a psychopathic personality in a previously normal subject may be almost the only evidence of earlier cerebral illness. Usually, however, neurological residual signs can be detected. The appearance of the Parkinsonian syndrome, with mask like face and rigidity of the limbs, should make the diagnosis easier. Oculogyric crises, i.e. recurrent spasms of the ocular muscles, and permanent difficulty in convergence are characteristic signs. In children, nocturnal excitement occurs together with inversion of the sleep rhythm.

Owing to their lack of self control and the unpredictable onset of their passions, combined often with an attractive personality, post encephalitic defectives are among the most tragic cases of mental defect. They may be dangerous to themselves or to others although the mental impairment is usually mild. So far as is known, there is no hereditary predisposition.

## CHAPTER XII

### DIAGNOSTIC AIDS AND TREATMENT

*General Principles—Case Histories—Technical Aids to Physical Diagnosis—Comparison with Normal Infant Behaviour—Psychological Tests—Specific Medical Treatments—Psychological Training—Eugenic Prognosis—Preventive Treatment—Positive Findings*

#### GENERAL PRINCIPLES

THERE are three possible objectives of medical treatment in mental subnormality—cure, alleviation and prevention. The emphasis on one or another depends upon limitations imposed by the nature of the particular case under treatment. In the interests of efficiency as accurate a diagnosis as possible has first to be made. In mental deficiency practice diagnostic investigations have to be made in two separate fields—the physical and the psychological—and the results combined.

#### CASE HISTORIES

Much depends upon an accurate case history. This must include a record of maternal health and the elements of a pedigree investigation in every case. Often it is desirable though not always practicable to make careful clinical examinations of other members of the patient's family.

The most important facts to obtain in routine family history work are ages, preferably the dates of birth, with mental status and general health reports on the parents and all sibs of the patient. The occupational and educational status of each of these relatives, as well as any interesting physical peculiarities, can be usefully noted down. Miscarriages and stillbirths must also be carefully recorded. Consanguinity of any type in the parental and grandparental generations always has to be enquired about and an exact record made of any interrelationship discovered. It is much more important to obtain accurate data on every patient's sibship and other close relatives than



it is to make elaborate pedigree studies in a few selected cases.

Details of maternal health are relevant to the patient's own life history during the embryonic and foetal stages. The circumstances of the patient's birth, neonatal condition and infantile development are particularly important, though they are often difficult to ascertain with accuracy. In all cases of mental defect it is of primary interest to know whether the defect has developed in a subject who was previously apparently normal. Moreover, the condition may be stationary, it may have improved or it may have been progressing unfavourably. Parents have to be most carefully questioned on these points and hospital records must be consulted whenever possible.

#### TECHNICAL AIDS TO PHYSICAL DIAGNOSIS

In earlier days it was often considered sufficient to wait until a patient died before making a careful pathological investigation. With modern methods of care, even low-grade patients live for a long time and it is desirable to obtain the maximal amount of information about each case as it comes under observation. Apart from routine procedures, like chest X-ray for excluding tuberculosis, and ordinary medical examination, there are numerous special techniques particularly adapted for studying defectives.

A defective child is more difficult to examine clinically than a normal child because it may be impossible to obtain the patient's cooperation. In low-grade cases neurological tests are almost confined to measurement of muscle tone and eliciting reflexes. Ophthalmoscopic examination is also troublesome, but its findings are objective and extremely important. Unsuspected optic atrophy, coloboma of the chorioid, retinal degeneration or tumours may be found on examination of the fundi. The condition of the cornea may be the chief clue to diagnosis, as, for example, in congenital syphilis. Cataracts of unusual type may be found.

Many conditions can best be appreciated in X-ray plates. This is true of generalized osseous dystrophies, such as Morquio's syndrome and dyschondroplasia. The skull can be very usefully studied in lateral X-ray views; in these, the bony peculiarities characteristic of acrocephaly, microcephaly and hydrocephaly are easily detected and the shape of the sella

turcica examined. Intracranial calcification may be noted in naevoid amentia, toxoplasmosis and cytomegalic inclusion disease.

Pneumoencephalography has a place as a diagnostic instrument in cases of severe defect. After displacing the cerebrospinal fluid with air by lumbar puncture, the outlines of the cerebral cortex and of the lateral ventricles can be seen by use of X-rays. The process is claimed not to be dangerous if competently carried out, with surgical precautions, preferably under anaesthesia (Levinson 1947). When cortical atrophy is present, its degree and location can be estimated. The method is useful for detecting hydrocephaly, arachnoiditis, subdural haematoma and cerebral abscess as well as tumour. Characteristic pictures are shown in several specific types of defect (Maurer, 1939, Delay, Desclaux and Pichot, 1947).

Electroencephalography, a technique developed out of Berger's (1929) discovery that the quiescent brain normally produces rhythmical electrical discharges which can be measured, has a limited application in mental deficiency practice. It is very difficult to obtain satisfactory results with this technique unless the patient is fully cooperative. The chief importance of such investigations in the mentally defective probably lies in detecting potential epileptics among higher-grade cases. Some psychopathic patients, admitted to hospital on account of behaviour disorders, may prove on examination to be subject to subclinical petit mal attacks. Kreezer (1939) made investigations of cerebral rhythms in several types of defectives and observed abnormally slow occipital "alpha" rhythms in some low-grade cases; the abnormal alpha rhythms were attributed to immature cerebral organization. No very characteristic pictures were obtained in mongols and phenylketonurics, for example. In tuberosc sclerosis also, Harvald and Hauge (1955) found no characteristic electroencephalograph pattern. On the other hand, Cobb, Martin and Pampiglione (1952) suggested that random, sharp transients on a background of generalized slow waves, in an epileptic, backward child, makes the diagnosis of cerebral lipoidosis very probable.

Examination of the urine for abnormal constituents has had special interest since the discovery of phenylketonuria. The development of chromatographic methods (Williams, 1946) and

other specialized biochemical techniques has made possible new investigations of the urine and other body fluids. This has led to the discovery, in recent years, of a number of genetically determined disorders of metabolism, particularly of amino acid metabolism which can result in mental defect (see Chapter VII). Such investigations are applicable also in attempts at detection of apparently normal carriers of some of these metabolic diseases. In addition, tests for the excretion of hormones may help to suggest the possibility of endocrine therapy as well as to define clinical types. A clearer definition of different types of defectives has been attempted also by investigations on blood chemistry. Since the earlier studies by Bixby (1940), on mongols, and by Kondritzer (1940), on phenylketonurics, much information has been collected. Electrophoretic methods have proved useful in determining serum protein and lipoprotein values in groups of retarded patients, for example in phenylketonurics (Stern and Lewis, 1958b).

The techniques of serology, which have advanced very rapidly in recent years, have much to contribute in the future to the field of mental defect. The search for maternal and foetal incompatibility necessitates taking samples of blood both from the patient and from his mother. Typing of the sera of patients, of their sibs and of their parents may eventually help to locate upon particular chromosomes the genes responsible for defects. When fairly close linkages are found, these will be used to help in the diagnosis of abortive or mild cases of known hereditary diseases.

The major progress in human cytogenetics, which has been made in the past few years, has a special bearing on the field of mental defect, intellectual retardation is a feature in many types of patient with chromosome aberration (see Chapters VIII and IX). Culture of cells derived from peripheral blood is an important technique for the study of human chromosomes. A convenient method is described in Appendix 10.

#### COMPARISON WITH NORMAL INFANT BEHAVIOUR

Since the diagnosis of mental defect is primarily a question of behaviour, the psychological examination of the patient is critical. There are many modern technical devices which can be employed in the diagnosis of mild or high grade cases,

where determination of the level of intelligence as exactly as possible is a matter of great practical importance. Among severe or low-grade cases, the ascertainment is useful for planning care and training and has significance also from the biological and genetical points of view.

If a subject's ability does not reach beyond the mental age of 2 years, few standardized tests can be effectively employed. Reliance has to be placed upon observations of behaviour to determine the mental level of an idiot as compared with the normal. Thus, the defective who has not begun to talk, walk or feed himself must be rated at less than 1 year. Those between 1 and 2 years in mental age can make an attempt at walking and feeding and respond to habit training. More precise estimates of mental age can be made for idiots by reference to Gesell and Amatruda's (1941) norms of development or to the Griffiths Mental Development Scale (Griffiths, 1954) standardized on English children. If information about the patient is indirect, the Vineland Social Maturity Scale (Doll, 1953) can be used. In all assessments, due allowance must be made for physical disability, especially when paralysis, blindness or deafness is a complication.

Before birth there are some signs which may suggest normality or deficiency in the foetus. Spontaneous foetal movement (quickenings) is normally felt by the mother towards the end of the fifth month of pregnancy. Absence of strong normal movements, or presence of foetal convulsions, may indicate maldevelopment of the nervous system. Anencephaly, hydrocephaly and some other osseous malformations can be demonstrated by X-rays.

The condition of the child immediately after its birth can be studied in order to exclude the diagnosis of idiocy or of imbecility, but not of mild mental defect. Signs of normality, such as crying, yawning, sneezing and stretching, can be observed in the first day of life. Discrimination of sweet taste and appreciation of cold temperatures are evident during the first 2 weeks.

The subsequent development of motor coordination can be summarized as follows. During its second month, the infant should attempt to lift its head when held on the shoulder, at 2 months it can hold its head erect for a few moments, and,

at 4 months, hold it steady when being carried. At 1 month, crawling movements are made when the child is laid prone on a flat surface, but, at 2 months in this position it can also lift the chest slightly. At 4 months, it attempts to sit up and stays sitting when supported. At 6 months, it can sit momentarily without support. At this age, too, it can roll from dorsal to prone position and can grasp, pick up and hold an object in either hand. At 9 months, it sits without support and, a little later, can pull itself up into a standing position.

At 1 year, the infant can lower itself from standing to sitting position and can walk with help. Standing and walking without help are established at 15 months and climbing stairs, or getting into a chair, is possible at 18 months. At this age also, a pencil is used spontaneously for scribbling and a tower of three blocks can be constructed. Ability to walk backwards is achieved at 21 months.

At 2 years the child should be able to run and to build a pile of six blocks; six months later, it can go downstairs alone and pile up seven or eight blocks. Tests with form boards become practicable at this stage and thereafter standardized performances can be measured or timed.

The development of language is of particular interest in the pattern of normal intellectual growth. An infant aged 1 month gives heed to sounds and in its cry is said to differentiate between expressions of pain and hunger. At 2 months, it attends to a speaking voice and may smile. Laughter is attained at 4 months and also elementary vocal response can be elicited. At 6 months, well marked vowels or syllables ("aroo" or "agoo") are produced spontaneously and familiar voices are recognized. Sounds like "da-da" or "pa-pa" are used to express pleasure at 9 months.

The child of 1 year should be able to say about two "words", that is, sounds which are attached to real situations or objects, and it also reacts to very simple commands. Four words should be enunciated at 15 months and about six words at 18 months. At this period the child can learn to point, on request, to its eyes, nose or hair.

At 2 years, the child can name objects or pictures of objects and, after 2½, has sufficient linguistic development to make possible the application of the Binet type of test.

In the first 2 years, and particularly in the first months, there are great differences in normal children. Variations in general health, nutrition and maturity at birth are significant causes of differences in rates of development. The defective child is generally supposed to develop in the same way as the normal but at a slower rate. This may not be always true. Irregularities in rate of development, as well as in the order of appearance of different achievements, are quite characteristic of infants both normal and defective. Consequently the diagnosis of mild intellectual defect is extremely difficult and unreliable in the first 2 years of life. Gross departures from the normal, such as occur in imbecility or idiocy, are usually unmistakable.

#### PSYCHOLOGICAL TESTS

After the age of about 2½ years, the standardization of achievement in normal infants becomes progressively more reliable. The cooperation of the child can be obtained and mental growth from that time onwards proceeds steadily. Techniques of many kinds for measuring mental abilities are available, though most of them do not deal very accurately with the pre-school level. Among tests which can be used for determining the mental level of imbeciles, theoretically down to a mental age of 2 years, are the Stanford-Binet scales (Terman and Merrill, 1937, 1961), the Merrill-Palmer scale (Stutsman, 1931) and the Minnesota Pre school Scale (Goodenough, Maurer and van Wagenen, 1940).

From the scholastic point of view educational level is predicted with fair accuracy by the various revisions of the Binet test. Many intelligence tests, which include pictorial, geometrical, numerical and verbal items, either in mixed order or in sets of similar items of increasing difficulty, can be employed for similar purposes. The Otis tests and the Kuhlman-Anderson scales are useful with high-grade or borderline cases. When dealing with defectives whose abilities are insufficient for them to be able to profit by ordinary school classes, manual dexterity and appreciation of shapes are tested by form boards and other devices, usually made of wooden blocks (Wallin, 1950). According to Pichot (1948), these methods originated in France and were developed by Seguin at Bicêtre. The manual performance tests most commonly used have been collected

and standardized by Arthur (1943) The use of words is not required in the solution of such tests, and so, for deaf children, gestures can be substituted for verbal instructions It is often remarkable how much better is the performance of hospital cases of all grades on manual tests than on verbal or numerical tests This may be partly due to the selection of cases for admission to mental deficiency hospitals that are scholastically retarded Careful psychometric examination can sometimes reveal hidden abilities in apparently quite low grade cases and in patients who suffer from deprivation of special senses Performance tests suitable for deaf children have been standardized by Drever and Collins (1944) and accurate information concerning the abilities of the visually handicapped has been obtained by Hayes (1941) with a modified Binet test Langan (1945) also adapted the Binet test for use with blind subjects The Peahody Picture Vocabulary Test (Dunn, 1959) provides a means for testing those with physical handicaps or speech impediments The high correlation found by Dunn between the Peahody test and the Stanford-Binet test has been confirmed by Mein (1962) using a severely subnormal group of patients

If the scores of a subject on different tests, verbal and performance, are all measured in general population standard deviation units, they can be expressed as a profile Irregularities of ability, which should be of much interest to teachers, can thus be clearly shown Uneven scoring on tests of various types, in different parts of the same test or sub tests of a battery is also a phenomenon of clinical importance Babcock (1930) demonstrated that a relatively high score on tests involving routine memory, such as vocabulary tests combined with a relatively poor score on tests involving adjustment to new situations, such as those requiring appreciation of absurdities, was characteristic of some mental illnesses Myers and Gifford (1943) have made use of this knowledge to set up a differential method of scoring the Binet Revision (Form L) Search for uneven performance of this type may be valuable in diagnosing psychopathic defectives Caution is needed in the interpretation of psychological profiles because there are normal differences between males and females More striking than this is the effect of age on the relationship between different abilities Vocabulary

lary tends to increase with experience, but ability to reason accurately in new situations decreases gradually in adult life. In addition to these points attention must be paid to the literacy and educational opportunities of the subject when a psychological profile is being studied. Wechsler (1958) has devised several test batteries, with separate verbal and performance scales to distinguish verbal from non-verbal intelligence. He also believes that the scatter of scores obtained on sub tests of these scales is useful for the diagnosis of various mental illnesses. Wechsler based his norms on the decline of certain mental abilities with age and in scoring the test responses, allowance is made for poorer performance with ageing. The Wechsler tests should not be used for subjects who have I Q below 50.

As further aids to the diagnosis of psychopathy in defectives, use may be made of association techniques. Heuyer and Courthial (1936) found that a considered judgment, based upon the results of questionnaires and association tests, agreed well with psychiatric diagnoses made by ordinary methods in 87 out of 114 children, attending a psychiatric clinic, some of whom were defective. The Rorschach Test or the Thematic Apperception Test can be valuable, but standardized responses, based upon those given by people of average intelligence, are not very helpful for defectives whose imaginations are less active than normal. Lack of response or stereotypy does not imply a disordered mind if the intelligence is limited. Again, inventories and questionnaires are also not very suitable for use with defectives because these tests fail to take into account the effects of varying intelligence level upon the answers. The chief value of all these techniques with defective subjects, and possibly also with others, is that they provide material which can conveniently be used at an interview to stimulate phantasy and thereby to produce information for the psychologist to interpret in the light of other knowledge.

#### SPECIFIC MEDICAL TREATMENTS

In so far as mental defect is not a disease but merely the expression of normal variation in the intellectual capacities of members of the human species, to speak of cure is absurd. The problem—which indeed arises acutely also in making



adequate provision for individuals of unusually high intelligence—is how best to make use of their qualities for the benefit both of the individuals concerned and of the rest of the community. The idea of cure as a medical aim is closely associated with the removal of a pathological condition. If a patient is admitted to a mental deficiency hospital on account of low scholastic capacity alone, it is the relationship of this individual to society that is pathological. Treatment in such cases aims at providing special educational and training facilities that will enable the patient to return to the community well enough equipped to be able to maintain himself satisfactorily thereafter. That this is not always possible may be the fault of society rather than of the individual. The rest of humanity may need to be cured in order to be able to tolerate the individuals concerned.

When low mental capacity is coupled with a mental or a physical disease, as is so frequently the case in hospital defectives, the radical cure of such a disease, on the assumption that in its absence the mental level would be sufficiently normal, is the primary aim of medical treatment. However, attempts have also been made to find some general treatment which may be expected to raise the intelligence level itself, almost regardless of the nature of the defect. For example, administration of stimulant drugs, such as caffeine and benzedrine, may temporarily improve test performance. Their continued administration, however, does not raise the intelligence level. Cutler, Little and Strauss (1940) and Moskowitz (1941) have reported experiments which indicate that benzedrine may have a little value as an aid to education in some cases. The physical condition is improved and the degenerative processes retarded, in some cases of myopathy, by administration of large doses of alpha tocopherol (vitamin E). In Hartnup disease, the pellagra-like skin rash may respond to nicotinamide.

Other forms of treatment, chemical and physical, have been used in an attempt to raise the intelligence level of defectives in general. Albert, Hoch and Waelsh (1946) drew attention to the therapeutic possibilities of feeding epileptic defectives on massive quantities of glutamic acid. Zimmerman, Burgmeister and Putnam (1948) have reported that an average gain of 6 to 8 points in Binet I.Q. is achieved in six months and that thereafter no further improvement is obtained. Though the initial

enthusiasm for glutamic acid administration subsided, favourable reports, for example by Foale (1952), continued to appear. However, Milliken and Standen (1951), on the basis of a well-controlled investigation, maintained that no effect at all is produced by glutamic acid treatment. Weil-Malherbe (1949) attributed a stimulating effect of glutamic acid to an adrenergic action which might be produced equally well by other amino-acids. Another interesting attempt at generalized cure has been unsuccessful, namely, the use of a preparation obtained from *Celastrus paniculata*, used for many years in India as a mental stimulant (Morris, MacGillivray and Mathieson, 1953). Cerebral ionization has been extensively applied by French physicians in the manner advocated by Bourguignon (1929). The treatment, as described by Chouraqui (1941), is periodically to pass an ionizing current through the cerebrum for some hours, after feeding the subject on calcium salts. Improvement in mental capacity, though not, of course, cure, has been reported in cases of diplegia, hemiplegia, mongolism and in other types of severe defect. The mental improvement was objectively demonstrated by an increase in the sensitivity of the vestibular nerve, measured by its chronaxie.

Variable results have been reported following the use of drugs with tranquillizing effects, such as chlorpromazine, serpasil and meprobamate, in disturbed, hyperactive defectives. They can have a beneficial effect on behaviour in some cases. Modification of the environment with appropriate occupational and socialization schemes also can produce similar effects, in a proportion of patients, without recourse to drugs.

The effect of treating mongol imbeciles by oral doses of pituitary hormone was reported by Benda (1953). The preparation contained a large amount of growth hormone and seems possibly to have some effect in increasing the size of the patients to whom it was fed. A slight increase in mental powers was also noted. Blumberg (1959) administered an oral pituitary extract, plus thyroid, to mongols. Good physical development was reported but an influence on mental growth could not be established. In recent years, siccacell therapy for mongolism has been advocated (Griffel, 1957), there is no satisfactory evidence of its value. The prospects of a cure for mongolism still seems remote.

More convincing therapeutically is the use of thyroid extract in cases of cretinism and particularly in juvenile subthyroidism with myxoedema. The good results of the treatment depend upon the lack of complications of thyroid deficiency. A child who is born a cretin may respond well physically to thyroid replacement therapy, but is unlikely to reach the average level of intelligence. If, however, the first signs of cretinism develop later, as in juvenile myxoedema, complete cure should be expected if continuous thyroid administration can be begun at once. Improvements have been noted in cases of pituitary dystrophy and even in mongolism after feeding the subjects on thyroid extract. However, this treatment is only effective in so far as thyroid deficiency is part of the clinical picture. Much physical harm can be done by the indiscriminate use of thyroid extract. Treatment of pituitary disorders by attempting to replace the missing hormones artificially has not been successfully applied to cases of mental defect. The possibility of improving low grade cases suffering from undeveloped gonads by supplying them with sex hormone substitutes, such as testosterone or stilboestrol, has not yet been fully explored. Overaction of the adrenal cortex in children is associated with abnormal sexual precocity and is occasionally accompanied by high intelligence, hence the effect on intelligence of injections of corticotrophic hormone seems worthy of investigation. Hemphill (1944) has summarized the possibilities of endocrine therapy in the psychoses, its application to cases of mental deficiency is still awaited.

In Wilson's disease, the accumulation of copper in the tissues indicates therapy with chelating agents in the hope of preventing or reducing degenerative changes. Dimercaprol (BAL) has been used with limited success. More recently, penicillamine has been shown to be of definite therapeutic benefit in many cases, it is usually more active than dimercaprol both in mobilizing copper and in promoting clinical improvement (Walshe, 1960).

Specific dietetic treatments have been tried in several types of mental defect. Many such experiments have been carried out on phenylketonuric patients, with the object of keeping the phenylalanine level in the body as low as possible, on the assumption that this substance is toxic in excessive quantities. Marked

even at intervals up to a year, can induce improvement and re testing at short intervals has a much greater effect. An increase of 2 to 4 points is obtained in the second administration of a Binet test within a few days (Terman and Merrill, 1937) and the Binet score is less subject to change in this manner than are the scores of most tests. Patterson (1946) has investigated the effects of re testing defectives with the performance tests which are included in the Arthur battery.

The most important work carried out in the field of training defectives is unspectacular. It is not highly technical but requires unlimited patience, good will and common sense. The reward is to be expected not so much in scholastic improvement of the patient as in his personal adjustment to social life. Occupations are found for patients of all grades so that they can take part as fully and usefully as possible in human affairs. This process, which has been termed socialization, contributes greatly to the happiness not only of the patients themselves but also of those who are responsible for their care.

Socialization programmes differ according to the grades of the patients concerned. Among idiots and imbeciles, besides ordinary habit training, a great deal can be done to encourage occupational interests. With children teaching still tends to follow lines laid down by Montessori and Seguin. A great deal of training at home is possible but, in many urban districts, centres for occupational classes are provided to relieve mothers of the care of defective children for a large part of the day. In a mental deficiency hospital much depends upon numerical strength and enthusiasm of the staff. When buildings and equipment are good, remarkable results can be obtained in creating a social life for low grade children. In such circumstances, Tizard (1960) reported gratifying results in a small group of imbecile children cared for and taught along residential nursery lines. *Adult imbeciles can also be provided with occupations and they will continue to carry out elementary tasks, which may appear intolerably dull, with the utmost diligence. Percussion bands and large sized toys have been successfully used for the amusement of adult idiots (Fitzgerald, 1938)*

The socialization of the feeble-minded encounters two distinct problems which arise on account of two distinct reasons for admission to a mental deficiency hospital, namely

scholastic inefficiency and social ineptitude. As far as possible, the hospital or special school must be a tutor, devoting special attention to the scholastic difficulties of feeble-minded children. As much reading, writing and arithmetic as the pupils can absorb is slowly presented in classes where competition with normal children is excluded. Melcher (1939) and Patterson (1947) recommend that scholastic learning should be regarded as incidental, not essential, for defectives. Manual skills can be more easily developed when tension, resulting from this obligation, is relieved.

Speech disabilities are much commoner in feeble-minded than in normal children; they occur in about half of all feeble-minded children and are universal among low-grade cases. As shown by Sirkin and Lyons (1941), there is considerable scope for special treatment of these defects, in high grade cases, with a view to increasing self confidence as well as economic fitness. Occasionally high-grade females have ability in linguistic matters, and when this is so, elementary teaching of foreign languages may give them useful exercise (Angiobillo, 1942). Acting in plays, singing and reciting all have their value in speech training. Feeble-minded subjects of both sexes often have artistic talents and these should be given every opportunity for development.

The importance of games and sports, as well as that of organized clubs, such as Boy Scouts and Girl Guides, has been rightly emphasized. In early times religious teaching was considered to be particularly valuable. A great variety of occupations, which tend to foster in the patients a sense of social usefulness and responsibility, have been successfully incorporated into training schemes. Defectives are not naturally antisocial. They are naturally very friendly and are particularly susceptible to influence during the formative years. There are good prospects for scholastically retarded children, whose special education is taken in hand early in the school period, and who are not exposed to social environments conducive to the development of behaviour difficulties.

In consequence of the neglect by communities to provide the most favourable educational facilities for feeble-minded and borderline children, the majority of high-grade defectives admitted to mental deficiency hospitals have already developed

antisocial tendencies. Thus a problem, quite separate from the primary educational one, confronts those who have care of them, namely, the re-education and rehabilitation of neurotics and psychopaths. The occupational programmes already planned for the training of defectives, who are not mentally disturbed, are also valuable for psychopathic subjects, but are insufficient. They are often on too juvenile a level for the relatively sophisticated high grade patients to appreciate, many of these may resent detention with those who are intellectually their inferiors. Some of these cases of behaviour disorder require the employment of the highest degree of psychiatric skill, but the routine duties of medical staffs in charge of defectives often leave little opportunity for this kind of work. The correct treatment of defectives who have become neurotic, psychopathic or delinquent is still largely an unsolved medical problem.

Attention is being given to problems of training from the point of view of preparing the patient to be a useful citizen outside, rather than inside, the mental deficiency hospital. Daily outside employment for high grade patients is helpful in this respect (Rohan, 1954), it broadens the character and teaches patients to mix with ordinary people. Workshops also can be used as experimental preliminaries to successful gainful employment (Tizard, 1953, Rockower, 1953). The occupational adaptation of high grade patients has been studied intensively by Tizard and O'Connor (1952). Very careful testing is recommended so that the subject's aptitudes as well as his latent abilities may be fully recognized. Tizard also has emphasized the importance of psychiatric treatment as an adjunct to manual or intellectual training and he recommends using group therapy. It is clear that the emotional state is an important factor in success or otherwise of educational efforts (Kanner, 1952), and that the atmosphere of a well run hospital can be conducive to significant improvements in mental ability as measured actually by standardized tests (MacMahon, 1952).

#### EUGENIC PROGNOSIS

Not infrequently relatives of a patient ask what are the chances that their future children will suffer from the patient's condition. The relative who enquires is commonly a parent

or a sib of the patient. In the light of present knowledge on human genetics, fairly accurate estimates can be given in particular cases, though these instances are likely to be rare. For a condition known to be due to a rare dominant with full manifestation, the task of making a prognosis for a future generation would be simple. The offspring of an affected person each have half a chance of being likewise affected, an unaffected person cannot transmit.

There are two main difficulties with a rare dominant, like that for epiloia, which usually present themselves in practice. These are due to irregular manifestation and to mutation. If manifestation were an all or none process, it would be feasible to multiply the probability of a child's carrying the gene by the manifestation to obtain a more accurate estimate. Such a method is unreliable because, if manifestation is altered by genetic modifiers, it will vary in different families. When modification is expressed by differences in age of onset, the difficulty can be easily appreciated. The sib of a Huntington's chorea patient, for example, cannot usually be known with certainty to be affected or unaffected until middle life is reached. The prognosis for his children becomes more favourable with every year that passes so long as he is without signs of the disease. Attempts are still being made to detect very early signs of the disease, and, if these prove successful the accuracy of prognosis will be greatly increased (Minski and Guttman, 1938, Patterson, Bagchi and Test, 1948).

It is easy to allow for the effect of new mutation on the prognosis for near relatives in a disease due to a fully manifesting single gene. Assuming that dyschondroplasia is a disease of this sort, Mørch (1941) points out that if both parents of a case were unaffected, the prognosis for their subsequent children, for the children of their normal sons and daughters and for their nephews and nieces would be equal to the incidence of the disease in the general population. In irregularly manifesting dominant conditions, the convenient assumption that a sporadic case is due to new mutation cannot safely be made.

The prognosis for relatives of patients with recessively determined defects can often be given with considerable accuracy. Degrees of manifestation are seldom of importance and the frequency of carriers in the population can be estimated

Parents who have already had one phenylketonuric child can be informed that the chance of another similar child is one in four. The unaffected sib of a phenylketonuric has two chances in three of being a heterozygous carrier and provided that he does not marry a cousin his chance of mating with a carrier is only about one in 100. The unlucky chance of both parents being carriers is thus only  $2/3 \times 1/100$ . Since, even then, only one child in four will be affected, the chance that any unaffected sib of a phenylketonuric patient will have a phenylketonuric child is  $1/4 \times 2/3 \times 1/100$ , or  $1/600$ . This is not a very serious risk and, for more distant relatives the corresponding risk is negligible (see also p. 155).

The special case of sex linked inheritance leads to the specific prognosis in the usual example of an affected son of a carrier parent, that half the subsequently born sons will be affected. Half the daughters, like their mothers, are carriers. The same prognosis can be given for fully sex limited dominants causing severe defects. The prognosis for sex linked diseases is improved if there is evidence that the mother is not a carrier and that the case has arisen by mutation.

Whenever a chromosome anomaly is found in a patient, close relatives should be carefully investigated for abnormal karyotype before any prognosis is given. In the majority of instances, parents will be found normal and the risks of repetition of the abnormality are likely to be small. There may be significant questions concerned with parental age which will have to be taken into account, however, in making an estimate. If a parent is shown to carry a balanced type of translocation, the risks of abnormality in children born subsequently may be considerable. At the present time it is not possible to lay down exact rules as the segregations of abnormal chromosomes are not necessarily in Mendelian proportions.

A common type of prognostic problem is presented by parents, both of normal intelligence, who have had one child of idiot or imbecile grade but with unspecified diagnosis. The risk of low grade defect for the children subsequently born to these parents can be calculated roughly on the basis of known sibships (Penrose, 1939d). Table XLVI (A) shows the classification of 1,897 sibs of 487 low grade probands whose parents were normally intelligent. Thus, some 2.8 per cent of sibs of low-



TABLE XLVI

MENTAL GRADES OF SIBS OF IMBECILE AND IDIOT PROPOSITI  
(Parents of Known Mental Grade)

Mental Grades of Sibs		Normal	Dull	Feeble-minded	Imbecile or Idiot	Total
Mental Ratios of Sibs		85 and above	70-84	50-69	Below 50	
(A) Parents of normal intelligence (487 propositi)	Number	1715	99	31	52	1897
	Percent	90.4	5.2	1.6	2.8	100.0
(B) Consanguineous parents of normal intelligence (14 propositi)	Number	39	1	2	7	49
	Percent	79.6	2.0	4.1	14.3	100.0
(C) One or both parents of subnormal intelligence (138 propositi)	Number	280	101	78	54	513
	Percent	54.6	19.7	15.2	10.5	100.0

grade cases are likely to be of the same low mental grade. As compared with the incidence in the general population, this is almost a tenfold increase (see Table IX, p. 50).

If parents are normal and consanguineous, the likelihood, that a low-grade defective child of undetermined type is the result of recessive inheritance, affects considerably the risk of repetition of low-grade defect in the sibs. According to the small group of sibships pooled in Table XLVI (B), the risk is 14.3 per cent. In the case where two idiots or imbeciles have been born to normal unrelated parents the risk is of the same order.

When one or both of the parents are of subnormal mentality, i.e. with mental ratio less than 85, and one low-grade defective has been born, the chance that another child will be of equivalent grade is about 10 per cent. As shown in Table XLVI (C), the risk of mild defect in such a sibship is also considerable.

Eugenic prognosis, where degrees of mental ability within the range of mild defect and normality are concerned, can be estimated roughly on the basis of the additive gene hypothesis. The mean intelligence of the children will approximate to the average level of the two parents, i.e. the mid-parental value. The expected range of variation in the children is difficult to

(1932) Since it is not known how many children would have been socially incompetent if the sterilizations had not been performed, the net social and biological achievement is hard to estimate. A carefully compiled evaluation of the results of applying such methods in North Carolina has been set down by Woodside (1950). Between 1929 and 1947, 349 males and 1,477 females had been sterilized, 58 males castrated and 17 females ovariectomized. In spite of numerous legal safeguards, the procedure leaves something to be desired. The measures are far more frequently applied to defectives than to any other class of case. Since the number of mentally deficient people in North Carolina is alleged to be 71,000, the sterilization of 100 cases in each year is unlikely to have any eugenic effect even if the crude assumption that like breeds like were true. In Germany, where a very large number of sterilizing operations were carried out in a brief space of time after 1933, the majority of defectives so treated were inmates of institutions and unlikely to have had offspring. An account of the working of the Danish sterilization laws has been given by Kemp (1946), and that of the Swedish laws by Weintraub (1951). Sometimes sterilization or even castration, has been used as a punitive measure. From the scientific point of view this is to be strongly deplored, as, indeed, is also the possibility of political bias entering into the selection of cases for this operation.

The recommendations of the Broek Report (1934) were greatly influenced by the view that sterilization should be a therapeutic attempt to aid those who had good grounds for believing that they might have defective children. A voluntary measure of this kind, however, might become essentially compulsory in cases of defect where sterilization was an alternative to institutional confinement. Against this, it has also been frequently asserted that sterilization helps defectives in their social adaptation because it limits their responsibilities. For example, according to Mickelson (1947) sterilization of feeble minded parents is beneficial to the children already born to them. Other authorities believe that sterilization encourages immorality. From the biological point of view the effects of limited use of voluntary sterilization are likely to be negligible, though considerable medical and social advantages might be obtained by its use in carefully picked individual cases.

It is difficult to justify compulsory sterilization of defectives on genetical grounds. However, if it were granted that all individuals with I Q below 70 should not be parents, there would still be great problems set. No tests of intelligence are accurate to 1 per cent and there is no natural boundary at I Q 70. It is absurd and unfair to apply an all or none measure to a continuous distribution, like that of intelligence.

The majority of parents of children with known recessively determined defects are normally intelligent, so there should be no difficulty in instructing them in contraception after the birth of a child affected in this way if they so desire. The development of methods for the detection of heterozygous carriers, as in phenylketonuria for example, could make it practical, though not necessarily desirable, to give such information to prospective parents of defective offspring before conception of any affected children. The same could apply to a mentally normal parent with sebaceous adenoma, for example. The peculiar maternal age distribution of many severe foetal abnormalities including mongolism, shows that a great reduction of their incidence could be brought about if pregnancies at the extremes of maternal age were avoided. Healthy prospective mothers could be encouraged to have their offspring between the ages of 22 and 30 in order to minimize the risks of foetal malformation. This age range is also the most favourable from the point of view of maternal health. Actually, the tendency to limit families which has affected both Europe and North America during several decades has reduced the births in the later more than in the earlier maternal age groups. If this process were to continue a reduction in the proportion of births resulting in mongol imbeciles and hydrocephalics could confidentially be predicted (Beall and Stanton, 1945).

The objection is sometimes raised against contraception as a eugenic instrument that it is only used by conscientious and, therefore, by comparatively eugenically desirable parents. A better understanding of the risks involved in specific cases which are often not so much greater than those to which every pair of prospective parents is exposed, may help to remove this danger. A new approach to the whole problem of negative eugenics is being made by the experimental use of oral contraceptives. Among the possible methods of preventing fertiliza-

tion, examined by Pine (1952) the most ingenious are those which act by inhibiting hyaluronidase, the enzyme which normally enables the sperm to get through to the ovum. Experiments on a volunteer population with a harmless substance, phosphorulated hesperidin by Sieve (1952) provided a promising start on this problem. More recently, studies have been made on the contraceptive effects of oral steroids taken by women (Eckstein, Waterhouse, Bond, Mills, Sandilands and Shotton, 1961, Mears 1961). The time may not be very distant when conception during any specified period can be prevented simply by a dose taken by mouth. Such a treatment could be used by people of low mental capacity much more easily than the methods which are recommended at birth control clinics at the present time. They would be preferred greatly to sterilization, both on the principles of humanity and of expediency.

The use of abortion for eugenic purposes has attained legal status in Denmark and is permitted when a feeble minded female is pregnant. There are occasions when this may be an obviously humane proceeding. Furthermore, with the routine use of X rays in pregnancy, anencephaly and some other types of gross cranial abnormality can be detected in the later months and premature labour may be induced, though it is standard obstetrical practice to allow such pregnancies to continue until near term. Since the majority of grossly abnormal foetuses die soon after birth, the medical question is usually limited to how best to treat the mother.

Infant mortality is high among idiots and imbeciles, but many of them continue far into adult life. The object of medical science in civilized communities is to keep people alive. This principle has no exceptions and it applies also to low-grade defectives of all kinds. Nevertheless, it has not infrequently been argued that, on humanitarian grounds a return to the methods of the Spartans is desirable, though of course modern society insists upon the term "euthanasia". The case for painless destruction of low grade defectives has been ably set out by Kennedy (1942), who claimed that it was justified by aesthetics, medicine, morals, convenience and common sense. In reply, the idiots' right to live was brilliantly pleaded by Kanner (1942). Not only are these low grade defectives harmless, they are not responsible for their own condition, they

can be happy and they can stimulate human feelings and parental love. By all canons of civilized society, they have a right to demand care and comfort even if they are unable to give adequate returns. The ability of a community to make satisfactory provision for its defectives is an index of its own health and progressive development, the desire for their euthanasia is a sign of involution and decay of human standards.

#### POSITIVE EUGENICS

It has been one intention, throughout this book, to explore the broad problems of eugenics and to show that they cannot be solved until the mode of action of natural selection on the human race is much more fully understood than it is at present. It may be relatively easy to point to genes which appear altogether bad, for example, those which make their possessors victims of epiloia or of Huntington's chorea. Even these may not be unfavourable in all circumstances. Carriers of "bad" genes may sometimes have compensating advantages.

The position is quite different when we try to identify "good" genes. The human types which are accepted by eugenicists as desirable can be specified to some extent. Good general health, handsome physique and high fertility, coupled with such qualities as great intellectual ability, courage, honesty, compassion and steadfastness are all desired in the same individual. Nothing is known, however, about the actual genes which might form the basis of such qualities. All that is certain is that some of these qualities are to some extent inherited. Assuming that excellence in each quality is not incompatible with excellence in any other, it should be theoretically possible, as Galton (1869) believed, "to produce a highly gifted race of men by judicious marriages during several consecutive generations."

That evolution in civilized man was subject to a great variety of social agencies, which did not apply to animals and plants, was clearly understood by Galton. Subsequently, Pearson (1909) after examining the same problems, asserted that civilization, by allowing the unfit to survive, was suspending the process of natural selection. It can be argued that the function of eugenics is to compensate for the biological errors of social life. This aim seems to underestimate the potentialities of biological adaptation. The human species is very variable

and variation within the species is favourable for long term survival, Fisher (1930) called this variance the "energy" of the species. Given sufficient energy, the human race should be able, even without the aid of eugenics, to adapt itself biologically to civilized life without risking extinction. The opposite view is to call every heritable deviation, from a theoretical optimal type, undesirable load (Muller, 1950).

Practical positive eugenics depends first upon finding out the manner of inheritance of desirable qualities. If it should be discovered that they are caused by genes in homozygous form, then the traditional methods of establishing pure lines by inbreeding, used by animal fanciers, could be encouraged. A race of men might eventually be produced in which almost every individual had all the best qualities. Apart from the danger that such a group might be relatively infertile, its possibilities of further evolution would be greatly limited. Its facilities for adaptation to new environments would be weakened because the collectively desirable quality of variation would have been deliberately reduced.

If, on the other hand, desirable qualities should prove to be produced by genes in heterozygous form, quite different methods of breeding would be favourable to their increasing prevalence. Maize is commonly grown from seed which is obtained from crossing two different pure lines, because the heterozygous plant grows more vigorously and produces more yield than either homozygous type. Whatever the system of mating, there is an upper limit to the total proportion of heterozygotes that can be formed at each generation among the offspring of a complete population. For a single pair of alleles, the maximal proportion of heterozygous offspring is two thirds but, with more alleles, there can be more heterozygous types. In human genetics there are some indications of heterozygous vigour in the increased fertility which accompanies slightly less than the average amount of scholastic ability.

It is abundantly clear that, in the present state of knowledge concerning human genetics, the prospects of positive eugenics, in the sense hoped for by Galton, are extremely narrow. Advances are continually being made in genetical science and in knowledge of the relationship of genetical constitution to environmental stresses. Notwithstanding, even when the

scientific knowledge of human heredity eventually becomes as complete as that of some experimental animals and plants, the utmost caution will be required in its application. The central problem, of what types of human beings are required, involves an insight into the future which at present we do not possess. The ultimate aim will have to be to compromise between the maximal vigour of the phenotypic population and its maximal potentialities for the future.

Against this background, the study of mental defect will continue to hold an extremely important place in the fields of medicine, psychology and genetics. The idiot, in earlier times alternately despised as an outcast or venerated, now is seen as an integral part of the human race in its struggle for evolution and survival, unwittingly yielding information of the greatest value in the progressive understanding of the biological structure of the whole group. High grade and borderline mental defect are phenomena which have come into prominence only since human life has become urbanized and industrialized. Civilized communities must learn to tolerate, to absorb and to employ the scholastically retarded and to pay more attention to their welfare. Subcultural mentality must inevitably result from normal genetical variation and the genes carried by the fertile scholastically retarded may be just as valuable to the human race, in the long run, as those carried by people of high intellectual capacity.

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# APPENDICES

## APPENDIX 1

### CRANIAL CAPACITY AND INTELLIGENCE LEVEL IN ADULT DEFECTIVES—MALES

Cranial Capacity	Intelligence Quotient										Total
	(0)	(10)	(20)	(30)	(40)	(50)	(60)	(70)	(80)	(90)	
2000 to 2099	—	—	—	—	—	1	—	—	—	—	1
1900 to 1999	—	—	—	—	—	—	—	—	—	—	—
1800 to 1899	—	1	—	—	—	—	—	—	—	—	1
1700 to 1799	—	1	3	1	1	—	—	—	—	—	6
1600 to 1699	2	2	1	1	5	4	2	—	2	1	20
1500 to 1599	—	9	9	7	8	10	9	8	1	2	63
1400 to 1499	2	11	16	14	14	25	21	17	3	2	125
1300 to 1399	2	16	12	18	16	26	27	10	6	—	133
1200 to 1299	3	8	8	3	10	16	5	6	3	—	62
1100 to 1199	1	7	4	3	5	5	1	—	—	—	26
1000 to 1099	—	—	—	—	1	—	—	—	1	—	2
900 to 999	—	—	—	—	—	—	—	—	—	—	—
800 to 899	—	1	—	—	—	—	—	—	—	—	1
Total	10	56	53	47	60	87	65	41	16	5	440

### CRANIAL CAPACITY AND INTELLIGENCE LEVEL IN ADULT DEFECTIVES—FEMALES

Cranial Capacity	Intelligence Quotient											Total
	(0)	(10)	(20)	(30)	(40)	(50)	(60)	(70)	(80)	(90)	(100)	
2000 to 2099	—	—	—	—	1	—	—	—	—	—	—	1
1900 to 1999	—	—	—	—	—	—	—	—	—	—	—	—
1800 to 1899	—	—	—	—	—	—	—	—	—	—	—	—
1700 to 1799	—	—	—	—	—	—	—	—	—	—	—	—
1600 to 1699	—	—	—	1	—	—	—	—	—	—	—	1
1500 to 1599	—	1	—	—	1	1	—	1	—	—	—	4
1400 to 1499	1	2	2	3	3	5	5	1	—	—	—	23
1300 to 1399	—	4	7	5	10	16	8	16	3	1	1	71
1200 to 1299	1	6	6	5	16	25	21	13	7	3	1	104
1100 to 1199	—	11	7	5	6	22	10	7	2	3	1	74
1000 to 1099	3	10	7	3	10	5	5	3	—	—	—	46
900 to 999	1	—	—	2	2	—	—	—	—	—	—	7
800 to 899	1	—	—	—	—	—	—	—	—	—	—	1
Total	7	34	29	24	49	76	49	41	12	8	3	332

(0) signifies the range 0 to 9, (10) signifies 10 to 19, etc. Correlation of male cranial capacity and intelligence quotient,  $r = +0.088 \pm 0.047$

Correlation of female cranial capacity and intelligence quotient,  $r = +0.176 \pm 0.034$

Cranial capacity is calculated from measurements, in millimetres, of length,  $l$ , breadth,  $b$ , and height,  $h$ , by the following formulae

Cranial capacity for males =  $(l-11)(b-11)(h-11) \times 0.000337 + 406.01$

Cranial capacity for females =  $(l-11)(b-11)(h-11) \times 0.000400 + 206.60$

## APPENDIX 2

APPROXIMATE MEAN HEAD MEASUREMENTS OF NORMAL SUBJECTS (Berry and Porteus, 1920)

	Year of life	Length	Breadth	Height
Boys	At birth	120	96	98
	1st	151	126	112
	2nd	166	130	116
	3rd	172	136	120
	4th	174	137	122
	5th	176	139	123
	10th	183 $\pm$ 4	145 $\pm$ 5	126 $\pm$ 4
	15th	188 $\pm$ 6	149 $\pm$ 5	129 $\pm$ 5
Girls	At birth	120	96	98
	1st	155	123	111
	2nd	164	129	115
	3rd	167	132	120
	4th	169	134	122
	5th	170	135	123
	10th	178 $\pm$ 5	140 $\pm$ 4	126 $\pm$ 4
	15th	183 $\pm$ 6	144 $\pm$ 4	130 $\pm$ 5

Measurements are in millimetres and standard deviations range from 4 to 6 mm

Westropp and Barber (1956) have recorded head circumferences for boys and girls at intervals up to the age of 7 years. Barber and Hewitt (1956) measured the transverse and longitudinal diameters of the skulls of the same children.

# APPENDIX 3

## INTELLIGENCE QUOTIENTS OF A HOSPITAL SAMPLE OF DEFECTIVES (Colchester Survey, 1938)

Age in Years	Intelligence Quotient																					Total	Males	Females
	(0)	(5)	(10)	(15)	(20)	(25)	(30)	(35)	(40)	(45)	(50)	(55)	(60)	(65)	(70)	(75)	(80)	(85)	(90)	(95)	(100)			
(0)	—	3	1	1	7	7	7	—	1	1	1	1	1	2	—	—	—	—	—	—	—			
(5)	3	5	2	5	17	10	6	5	4	3	13	14	18	19	3	4	1	—	—	—	—			
(10)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—			
(15)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—			
(20)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—			
(25)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—			
(30)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—			
(35)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—			
(40)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—			
(45)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—			
(50)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—			
(55)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—			
(60)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—			
(65)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—			
(70)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—			
(75)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—			
Total	17	27	84	90	71	72	70	52	68	101	114	135	131	66	78	44	23	18	11	5	3			
Males	10	15	54	60	46	42	45	32	33	49	61	73	69	32	42	19	11	9	6	2	—			
Females	7	12	30	30	25	30	25	20	35	52	53	62	62	34	36	25	12	9	5	3	3			

(0) signifies the range 0 to 4, (5) signifies 5 to 9, etc

## APPENDIX 4

NUMBER OF PATIENTS RESIDENT IN MASSACHUSETTS STATE SCHOOLS FOR THE  
MENTALLY DEFECTIVE, compiled by Dayton (1939)

I Q	Males	Females	Total
0- 9	174	164	338
10-19	301	222	523
20-29	317	300	617
30-39	341	315	656
40-49	512	508	1020
50-59	461	549	1010
60-69	316	445	761
70-79	103	164	267
80-89	14	24	38
90+	2	6	8
Total	2541	2697	5238

There is a characteristic excess of males among severe cases and of females among mild cases

## APPENDIX 5

TABLE SHOWING PERCENTAGE OF FIRST-COUSIN PARENTAGE (F) \* FOR CASES WITH RARE RECESSIVE DEFECTS

Case Frequency	Gene Frequency	Frequency of First-cousin Matings in the General Population (x)		
		0.5 per cent	1.0 per cent	2.0 per cent
$q^2$	$q$	(F)	(F)	(F)
1/1 000	1/32	1.0	2.0	3.8
1/10 000	1/100	3.0	5.9	11.1
1/100 000	1/316	9.0	16.5	28.3
1/1 000 000	1/1 000	23.8	38.4	55.6

$$*(F) = \frac{100x}{\alpha + 16q}$$

N.B. If the defect did not decrease chances of parenthood, the correct formula would be

$$(F) = \frac{100x}{\alpha + 16q(1-\alpha)(1+15q)}$$

## APPENDIX 6

## CORRELATION TABLES FOR A METRICAL CHARACTER DUE TO A SINGLE AUTOSOMAL GENE PAIR

## (i) Parent and Child

Genotype	aa	Aa	AA	Total
AA	—	$p^2q$	$p^3$	$p^2$
Aa	$pq$	$pq$	$p^2q$	$2pq$
aa	$q^3$	$pq^2$	—	$q^2$
Total	$q^2$	$2pq$	$p^2$	1

## (ii) S b and S b

Genotype	aa	Aa	AA	Total
AA	$\frac{1}{2}p q^2$	$p^2q - \frac{1}{2}p q^2$	$p^3 + \frac{1}{2}p^2q^2$	$p^2$
Aa	$pq - \frac{1}{2}p^2q^2$	$pq + p^2q^2$	$p^2q - \frac{1}{2}p^2q^2$	$2pq$
aa	$q^3 + \frac{1}{2}p^2q^2$	$pq^2 - \frac{1}{2}p q$	$\frac{1}{2}p^2q^3$	$q^2$
Total	$q^2$	$2pq$	$p^2$	1

Measurements corresponding to the genotypes AA Aa and aa can be denoted by  $x$   $y$  and  $z$  respectively. If the heterozygote Aa is perfectly intermediate we put  $x=1$   $y=\frac{1}{2}$  and  $z=0$  and calculate the product moment correlation for both tables (i) and (ii) the result is exactly 0.5. If A is completely dominant and a completely recessive  $x=y=1$  and  $z=0$  the correlation in table (i) becomes

$$\frac{q}{1+q} \text{ and that in table (ii) is } \frac{1+3q}{4(1+q)}$$

## APPENDIX 7

TABLE OF NUMBERS REQUIRED IN FACTORIAL TEST FOR SIBSHIPS CONTAINING  
RECESSIVE ABNORMALITIES

$S$  = number of children in a sibship including an affected member  
 $S/4[1 - (1/4)^S]$  = expected apparent number affected in a sibship of size  $S$  on  
 the supposition that one-quarter of all children in such  
 families are affected. Note that in large sibships, the ex-  
 pected number closely approaches one quarter of  $s$

$K_S$  = variance of expected number of affected sibs in sibships of  
 size  $S$

$S$	$S/4[1 - (1/4)^S]$	$K_S$
1	1.000	0.000
2	1.143	0.122
3	1.297	0.263
4	1.463	0.420
5	1.639	0.592
6	1.825	0.776
7	2.020	0.970
8	2.222	1.172
9	2.433	1.380
10	2.649	1.592
11	2.871	1.805
12	3.098	2.020
13	3.329	2.335
14	3.564	2.446
15	3.801	2.658
16	4.041	2.867
17	4.282	3.074
18	4.526	3.279
19	4.770	3.481
20	5.016	3.682



## APPENDIX 8

## INTELLIGENCE QUOTIENTS IN SPECIAL TYPES OF HOSPITAL DEFECTIVES

Associated Disease	Number of Cases			Mean I Q	Standard Deviation of I Q
	Males	Females	Total		
Neurofibromatosis	4	2	6	67.8	9.5
Psychoneurosis	69	63	132	63.8	19.1
Craniofacial dysostosis	2	1	3	54.0	25.7
Post-encephalitic	10	11	21	53.9	26.6
Psychosis	43	29	72	48.2	24.0
Post traumatic	19	4	23	45.0	24.5
Congenital syphilis	23	27	50	42.7	19.8
Epilepsy	69	50	119	41.2	22.4
Congenital hemiplegia	8	3	11	36.4	14.4
Choreoathetosis	6	5	11	35.5	14.9
Hydrocephaly	5	1	6	32.0	19.8
Hypertelorism	2	5	7	31.7	18.2
Spastic diplegia	30	25	55	29.1	21.0
Acrocephaly	11	6	17	28.6	19.9
Microcephaly	18	5	23	24.6	14.8
Mongolism	41	22	63	22.8	7.9
Phenylketonuria	21	26	47	19.9	12.6
Epilepsia	2	3	5	11.8	10.7
Sample containing all types of patient (Appendix 3)	710	570	1280	40.4	25.6

APPENDIX 9  
MENTAL STATUS OF PARENTS OF 1280 PATIENTS (Colchester Survey, 1938)

Classification	Description	Number of Patients	Sexes of Parents	Number of Parents in each Mental Grade					Percentage of Parents known to be Defective
				S	N	D	F	Imb	Un-ascertained
By sex of patient	Male	710	Male	6	580	69	22	0	33
	Female	570	Female	2	521	103	65	2	17
By mental grade of patient	Male	433	Male	3	427	80	26	1	33
	Female	220	Female	0	380	99	78	1	12
By clinical type of patient	Borderline	179	Both	1	255	63	18	0	21
	Feeble minded	448	"	3	580	159	106	3	45
	Imbecile	433	"	4	687	92	55	1	27
	Idiot	220	"	3	386	37	12	0	2
By clinical type of patient	Mongolism	63	Both	0	119	5	2	0	0
	Endocrine disorder	88	"	2	135	24	9	0	6
	Congenital syphilis	50	"	0	75	9	6	0	10
	Neurological lesion	128	"	3	230	13	8	0	2
	Skeletal malformation	142	"	1	227	35	12	1	8
	Miscellaneous abnormalities	87	"	1	141	20	9	0	3
	Idiopathic epilepsy	210	"	2	321	52	29	0	16
	Non-epileptic mental illness	204	"	2	293	69	26	0	19
	Residual group	303	"	1	367	124	90	3	31
	All patients	1280	Both	11	1903	351	191	4	95
Total of each classification									7.6

S=Superior, N=Normal or average, D=Dull or borderline, F=Feeble-minded, Imb=Imbecile

Dilute 45 cc of this solution with 55 cc distilled water to make the stain ready for use

- 5 *Cresyl fast violet* (Gurr) 1 per cent solution in distilled water
- 6 *Glucose saline* dissolve 0.6 gm glucose and 0.7 gm sodium chloride in 100 ml deionized water. Sterilize in autoclave at 15 lb per sq in for 15 mins

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